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PHENOTHIAZINE—A REMARKABLY EFFICIENT ANTHELMINTIC

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Introduction

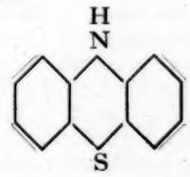
As the result of a publication by E. F. Knipling in April, 1938, reporting the extraordinary efficiency of internal treatment with small doses of phenothiazine for preventing the development of hornfly larvae (*Lyperosia irritans*) in the faeces of cattle, a brief trial on pigs was carried out at this laboratory in order to ascertain whether the drug might not also possess a marked anthelmintic action.* The experimental pigs used for this purpose were not very heavily infected and as the efficiency of the drug, as indicated by this trial, only proved to be between 0 per cent. and 60 per cent. nothing further was done until August, 1939, when news of the success of Australian workers reached us and a private communication was received from W. E. Swales giving an account of remarkably good results obtained by him in Canada for the elimination of worms from comparatively lightly infested sheep.

Fortunately, we were aware of a severe outbreak of parasitic gastritis within 20 miles of the laboratory at that time and still having in our possession a certain amount of phenothiazine left over from the previous trial in pigs were able to carry out an experiment forthwith, on heavily infected sheep. This trial produced a surprisingly good result and on reporting our findings to the Helminths Committee of the Agricultural Research Council it was decided that the Council should be asked to purchase some 500 pounds of the drug for the purpose of carrying out an extensive trial under farming conditions as speedily as possible.

The symposium of which this paper forms part, deals with work carried out in various parts of the country and co-ordinated through the Agricultural Research Council.

History of Phenothiazine

Phenothiazine is described by De Eds *et al.* (1938) as " a fine, smooth powder having a pale, lemon yellow colour, and is practically tasteless. When allowed to crystallize from solutions of alcohol, benzene, xylol, or toluol, flat leaf crystals with a soapy feel are formed. Phenothiazine melts sharply at 180° C., is soluble in fat solvents, but is practically insoluble in water. It has a molecular weight of 199·14, and the following structural formula :—



" When exposed to air and moisture, phenothiazine slowly undergoes spontaneous oxidation. It is the parent substance of a large number of dyes, the most important of which, as regards the present work, are the three thiazine dyes, thionol, Lauth's violet, and methylene blue." It was first prepared in 1885, by Bernthsen, but does not appear to have found any special uses nor was there any evidence of its parasiticidal properties until 1934 when Campbell *et al.* reported on its toxicity against culicine mosquito larvae. These trials showed it to be even more toxic than rotenone, its action proving to be quite effective down to a dilution of 1 : 1,000,000.

Smith, Munger and Siegler (1935) then tried it for the control of the codling moth and found it to be as effective as lead arsenate. Knipling (1938), however, was the first to report its marked action against parasites of domestic animals ; he fed small amounts to cattle and found that whereas no toxic effects were observed, the development of hornfly larvae (*Lyperosia irritans*) was completely inhibited in the faeces for three days. Harwood, Jerstad and Swanson (1938) then tried phenothiazine in pigs and found a rather variable, but nevertheless marked action not only against ascarids but also against oesophagostomes. Harwood, Haberman and Jerstad (1939) later reported observations on eight sheep, in which they found marked anthelmintic action at a dose rate of 1 gramme per kg. body weight, against hookworms and nodular worms and also against *Haemonchus* and *Ostertagia*, the effect apparently being particularly marked against *Ostertagia*. Swales (1939) next reported results obtained in the treatment of ten lightly infected sheep ; he perfected an effervescent tablet and found a dose of 0·6 gramme to 0·8 gramme per kg. body weight to have a very pronounced action against stomach worms, nodular worms and hookworms. Gordon (1939) in Australia, also published a note having found a dose of 0·2 gramme per kg. to have a variable efficiency against nodular worms, ranging up to 100 per cent. Along with Whitten (1939), he also published a short note reporting an

*The phenothiazine used on this and on a later occasion was very kindly supplied by the Imperial Chemical Industries workers on insecticides at Jealott's Hill. At that time the drug was difficult to obtain and without their help our early trials might have been considerably delayed.

efficiency of 100 per cent. against *Haemonchus*. Concurrent with this publication came one from Roberts (1939), another Australian parasitologist, who reported observations on seven lambs in which a dose of 0·2 gramme per kg. was shown to have an efficiency ranging up to 94·7 per cent. against nodular worms and more recently Swanson, Harwood and Connolly (1940) have reported trials in pigs in which they found doses of phenothiazine ranging from 5 grammes to 30 grammes, according to the size of the pig, to be very effective against nodular worms and ascarids, although less effective against light infections of ascaris than against heavy ones.

The results reported by the present authors concern more extensive trials on larger groups of animals most of which were actually suffering from helminthic disease at the time that the trial was carried out. Sheep and horses have been most largely used and results, almost without exception, have been extraordinarily good.

The phenothiazine used in these observations has been supplied by the Imperial Chemical Industries in four forms: (*a*) pure phenothiazine powder, having a purity of about 99 per cent.; (*b*) phenothiazine powder mixed with a wetting agent to facilitate its mixture with water; (*c*) liquid phenothiazine, being a suspension of very finely powdered phenothiazine in water containing some dispersing agent, and (*d*) phenothiazine tablets, containing 5 grammes of the pure drug and a certain amount of excipient together with a substance that brings about a rapid disintegration of the tablets when placed in water.

Experimental Data

Sheep

Anthelmintic Effect.

Experiment No. 1.—Eleven lambs, badly affected with parasitic gastritis, were purchased from a flock among which fifty had just died from this disease. On reaching the laboratory they were divided at random into two groups, five being kept as controls and six receiving 15 grammes of the phenothiazine mixture recommended by Swales.*

All of the lambs, controls as well as treated animals, were killed five days after the dosing had been carried out and worm counts were made on the stomach and intestinal contents. Results given in Table No. 1 show a very remarkable effect of the treatment in that no worms were recovered from the stomachs of the six treated lambs, mature *Ostertagia* and *Trichostrongylus* having been completely eliminated, whereas four of the five controls contained over 15,000 worms in the fourth stomach. The effect on worms in the small intestine was less striking but nevertheless demonstrated an efficiency of over 80 per cent.

Experiment No. 2.—When the outbreak of parasitic gastritis among the flock from which the above-mentioned eleven lambs had been purchased began to diminish, and deaths occurred less frequently, forty of the most severely affected of those still remaining alive were picked out for a further trial. They were divided at random into two equal groups, one of which received four weekly doses of phenothiazine, the other being kept as a control group.

Samples of faeces were collected for the purpose of making a composite count, and all of the lambs were weighed on each of the four occasions when dosing was carried out. Particulars are set out in Table III and demonstrate the effect of the drug during one month in bringing about an increase in weight of 2·2 lb. per head over and above the gain in weight of the untreated controls.

Experiment No. 3.—Concerns an outbreak of parasitic gastritis among a flock of 91 lambs of which 36 had already died before the experiment began.

The opportunity was afforded at the time that the diagnosis was made of examining the contents of the stomach of one of the lambs which had died of parasitic gastritis, and the infestation was found to comprise 20,750 *O. circumcincta*, 4,550 *T. axei* and 220 *H. contortus*.

The flock was then divided at random into two equal groups of 28 lambs; members of one group being given a dose of 20 grammes of phenothiazine in the form of a draught, without the additional substances used by Swales and the other group were kept as an undosed control. Weights and composite egg counts were made on the first and on two subsequent occasions and are shown in Table IV.

The result obtained in this observation was very remarkable in that the dosed sheep made an increase of 12 lb. per head over and above the increase in weight of the controls during the six weeks of the trial, representing a total increase of 336 lb.

Experiment No. 4.—There had been several deaths from parasitic gastritis among this flock during an outbreak of the disease which had occurred some twelve weeks previously. A *post-mortem* examination carried out at that time had shown the following parasites to be present: 23,940 *O. circumcincta*, 1,330 *T. axei* and 1,330 larvae in the stomach, and in the small intestine, 20,640 *T. vitrinus*, 1,290 *C. curticei*, 430 *C. oncophora*, 5,160 *N. filicollis* and 2,580 larvae. About 20 lambs had died and the remainder of the flock made a more or less satisfactory recovery before the test dosing was carried out on October 31st.

On this occasion the 30 poorest lambs were taken out of the flock of 400; these individuals were then selected in order, proceeding from the poorest to the best member of the group; two out of every three were dosed with 30 grammes of phenothiazine in the form of capsules, and the third was kept as an undosed control: all were weighed. The results, which are given in Table V, show an average increase during the three weeks observational period of 2·1 lb. per head among the treated lambs, over and above the average increase per head of the undosed lambs.

Experiment No. 5.—K. D. Downham of the Harper Adams Agricultural College reported an observation on eight lambs suffering from parasitic gastritis in which during the first six days after treatment the four dosed lambs made an average gain of 5·5 lb. each, whereas the four undosed controls made an average gain of only 1·5 lb.

Effect of the Dosing of Healthy but Infected Lambs.—The following few observations were carried out on healthy lambs to ascertain whether the removal of a relatively slight infestation of parasitic worms, not sufficient to cause obvious symptoms of disease, might bring about an increased rate of growth.

Experiment No. 6.—This observation, carried out by K. D. Downham, concerned 20 healthy lambs, all born in March, and picked out from a well-managed flock that had been periodically dosed with copper sulphate and received frequent changes of pasture throughout the previous summer. The lambs were divided into two equal groups the members of one of which received a dose of 15 grammes of phenothiazine on December 6th.

A second weighing carried out three weeks later showed an average increase of 0·7 lb. per head among the group of dosed lambs in excess of the increase among the controls.

Experiment No. 7.—Another collaborator, J. W. Ironside of the Midland Agricultural College, carried out

*Swales recommended a special mixture of phenothiazine of the following composition:—

Commercial phenothiazine (pulv.)	80 parts
Starch (pulv.)	9 ,,
Effervescent salts (sod. bicarb. 50 parts, dehydrated tartaric acid 45 parts)	9 ,,
Dried ox gall	2 ,,

a similar observation on ten healthy lambs, previously treated with copper sulphate and nicotine sulphate.

Results also showed a slight increase of weight in favour of the treated group which during four weeks gained an average of 10·4 lb. as compared with 9·8 lb. in the controls.

Experiments with Small Doses.—It was felt that the large size of the dose and the bulky nature of the drug threatened to be the most powerful factor operating against its general use in sheep and we, therefore, carried out a few trials to ascertain whether it might not be possible to secure adequate anthelmintic action with a much smaller dose. Results of the trials carried out on eight sheep are shown in Table VI and indicate that whereas doses of less than 3 grammes had no action, those of 3 grammes (0·08 grammes per kg. body weight) and over, produced a marked effect.†

Some further evidence of the minimum effective dosage is given in Table IX, which suggests that amounts as small as 1·5 grammes and 1·75 grammes had some effect.

Daily Doses of Phenothiazine Mixed with the Food.—Doses of 2 grammes, 5 grammes and 10 grammes were tried in three pairs of sheep, the phenothiazine being given in powder form mixed with the food. The results, which are given in Table VII, show considerable effect even for the 2 gramme doses, the 10 gramme dose, however, producing the result more rapidly.

The sheep receiving the 10 gramme doses did not eat their medicated food at all readily but those on the smallest dose took it well; and suffered no ill effect whatsoever; the two sheep receiving 10 grammes daily, however, began to show signs of intoxication after the first week, dullness and inappetence being the principal symptoms, and on the thirteenth day one of them died, showing diarrhoeic symptoms for a few hours beforehand.

Tolerance of Sheep.—Apart from the daily dosing of 10 grammes no evidence of the slightest toxic effect had been observed in any of the therapeutic treatments of sheep; in an endeavour to obtain some idea of the toxic dose, therefore, four lambs weighing between 86 and 89 lb. received 40 grammes, 80 grammes, 200 grammes and 400 grammes of phenothiazine respectively, but without any signs of intoxication being produced.

The absence of result from the top dose seemed so surprising that it was repeated in another lamb of the same weight, but again produced no ill effect whatever.

The lamb that died as a result of repeated daily doses refused food for the last day or two and showed a dark red diarrhoea before death;‡ this lamb was in a particularly poor condition when the treatment commenced, which may have had something to do with the fatal result; a second one in better condition, however, also showed signs of intoxication although it survived 16 daily doses of 10 grammes. Two other lambs which received daily doses of 5 grammes each showed no such symptoms.

Summary of Observations in Sheep.—Extensive trials suggest that in doses of 15 to 30 grammes (0·5 to 1 gramme per kg. body weight) phenothiazine has a remarkably good anthelmintic effect in sheep, the efficiency of its action ranging round 100 per cent. for worms in the fourth stomach and 80 per cent. for most of the worms in the small intestine. Where used in actual outbreaks of parasitic gastritis its effect is reflected in very considerable gain in weight.

†It is possible that the dose of 1 gramme given to these sheep four days previously may have helped to bring about the observed result. This possibility also applies to the results obtained in the goats, which had also received small doses two or three days previously.

‡*Post-mortem* findings in this sheep were as follows:—

Nasal passages filled with a catarrhal exudate of a pink colour, presumably due to the inhalation of phenothiazine powder, the mucous membrane over the turbinated bones and in the upper part of the trachea was of a dark reddish brown colour, but apparently not inflamed, the coloration presumably also being due to the formation of thionol from the drug. Bronchioles also contained much catarrhal exudate. Liver showed signs of fatty degeneration; the kidneys were of a dark red colour, the pelvis containing a brownish liquid. The fourth stomach showed a slight inflammation of the mucous membrane throughout its whole extent.

Less extensive trials suggest that doses as low as 0·08 gramme per kg. body-weight have a considerable anthelmintic effect although the action of larger doses is more reliable.

The tolerance of sheep is extraordinarily high, 400 grammes having been given without ill-effect; a repeated daily dose of 10 grammes, however, produced a fatal intoxication in one instance.

Sheep will take 2 grammes to 5 grammes mixed with the food, a good anthelmintic effect being produced even by the smaller dose.

Administration is best carried out by means of 5 gramme tablets and a rubber-ended balling gun.* Given adequate assistance it is possible for one person using a balling gun to administer a 10-gramme dose to 160 lambs in an hour.

Goats

Experiment No. 8.—The following observations were made on the effects of phenothiazine on a group of goats at the Ministry's laboratory, many of their number suffering severely from parasitic gastritis.†

Fifty-three goats were used for this experiment; 25 received one dose of phenothiazine in capsule form, varying between 10 grammes and 30 grammes according to the size of the goat, and 28 were kept as controls.

During the three weeks observational period the egg count among the 25 treated goats was reduced from an average of 5,080 to an average of 533, the egg count among the 28 controls falling from an average of 6,696 to 3,808 during the same period.

Several of the goats showed signs of intoxication for three or four days after the administration of these doses; they refused all food, looked dull, and were often seen to stand motionless in a corner of the stall with their heads hanging down.

As a result of the various origins of the experimental goats, and the small number of *post-mortem* examinations carried out, the results are less conclusive than they otherwise would have been, but they suggest that the drug acted particularly powerfully on *Ostertagia circumcincta* and on *Trichostrongylus axei,* less powerfully on worms in general in the small intestine and not at all on *Nematodirus filicollis, Moniezia* spp. and *Fasciola hepatica.*

The *post-mortem* results also suggest the 10 gramme dose to have been less efficient that the 20 and 30 gramme doses.

The Effect of Small Doses in Goats.

Experiment No. 9.—In this experiment eight goats received gradually increasing doses of phenothiazine at intervals of four days, the doses ranging from 0·5 gramme to 12 grammes. The data which were collected are shown in Table II and indicate that doses up to 1½ grammes are without effect; a dose of 4 grammes appears to have had some effect, 6 grammes had a decided effect, and the 8 gramme dose appears to have been just as effective as the 12 gramme dose given later. In one or two instances, however, the small doses failed to expel a considerable number of worms, notably in goat 428. These results conform with those of experiment 8 and it may be concluded that doses of less than 20 grammes, although effective, cannot be relied upon to produce the maximum anthelmintic action.

Tolerance of Goats.—In view of the signs of toxic action seen in several of the treated goats a series of

*In a private communication received since this was written, Dr. Robertson of the Aberdeen School of Agriculture claims to have dosed sheep with the liquid form of phenothiazine at the rate of four per minute. McEwen and Rowlands also preferred the liquid and as the tablets are very awkward to administer without the proper balling gun this form of the drug may be found to be the most generally useful.

‡These goats had been collected from various centres in Wales, and in Ireland, several of them being in a more or less advanced stage of parasitism on arriving at the Laboratory. On account of their different origins, therefore, the nature of their helminthic infections did not conform so nearly to one type as it would have done had they all come from one source.

trials was carried out in order to assess the toxic dose. In the first trial six goat kids were treated with 10, 20, 30, 40, 50 and 60 grammes respectively, of phenothiazine, but without producing any ill effect. Eight adult goats were next treated with 50, 60, 70, 80, 90, 100, 110 and 120 grammes respectively, but again without producing any ill effect.

Only three days later when it became clear that there was a negative result from the previous administration a dose of 400 grammes was given to the goat that had previously received 80 grammes, but even this produced no noticeable effect whatever.

Summary of Results in Goats.—Our observations suggest that at certain times goats may be less tolerant of phenothiazine than are sheep, but even at those times are good subjects for anthelmintic treatment with this drug. At other times they are able to withstand enormous doses, similar to sheep. Doses varying between 10 and 30 grammes reduced the egg count to one-tenth of what it was before treatment was carried out. A dose of 6 grammes reduced the infestation very considerably and an 8 gramme dose appeared to be in no way inferior to a 12 gramme dose.

Cattle

Experiment No. 10.—Concerned an outbreak of parasitic gastritis among seven Jersey calves in which two had just died at the time that the outbreak came to our notice. Egg counts made on samples of faeces collected from two dead calves on September 3rd gave a count of 3,900 and 1,500 eggs per gramme respectively, counts that are considered to be high for cattle. *Post-mortem* examination showed the presence of a pure infestation of *Ostertagia ostertagi*, 8,200 being recovered from the fourth stomach of one calf and 20,200 from the other.

Three of the five remaining calves were then treated with 25, 35 and 45 grammes of phenothiazine powder respectively, and the other two kept as controls. On September 13th the three treated calves were found to have improved in condition and to have recovered from the diarrhoea; one of the two controls, however, looked distinctly worse than on the previous occasion and so was given a dose of 30 grammes of phenothiazine. This animal died on September 20th, presumably having been beyond the hope of recovery at the time that treatment was given: *post-mortem* examination revealed the presence of only 200 *O. ostertagi* in the stomach and 600 in the small intestine. The remainder of the animals ultimately made a good recovery.

This observation appears to indicate the efficiency of 25 to 40 gramme doses of phenothiazine against *O. ostertagi* in calves.

Experiment No. 11.—Was carried out by W. J. Ironside of the Midland Agricultural College on six cattle which had previously received treatment with copper sulphate and nicotine sulphate.

The three treated cattle varied considerably in size but all received the same dose of 70 grammes of phenothiazine, as a result of which they were all very seriously upset and refused food for several days. One of the three, which was in a weak state at the time of dosing, became so ill that it was expected to die; but all ultimately made a good recovery.

The egg count per gramme of faeces in the treated cattle was reduced during the three weeks observational period from 800, 100 and 1,200 to 200, 0, and 0, respectively, whereas among the three controls the successive counts were 300, 1,300 and 700, respectively, at the first examination, and 400, 1,000 and 900 at the second.

Tolerance of Cattle.—The suggestion of susceptibility to toxic action given in *experiment* 11 led to our carrying out one or two direct observations on this point, and on October 26th a dose of 1,000 grammes was given in the form of a drench to a 14-weeks-old calf, it being anticipated that the tolerance of cattle might approach that of sheep. Within an hour the calf lay down and would not rise; on the following day it was found to be lying on its side, the temperature having risen to 102·4°, at which point it remained. Great muscular weakness was noted on October 28th and 29th, on October 30th respiration was observed to be rapid, the pulse was weak, and death occurred during the afternoon.

Post-mortem examination showed extensive ulceration of the mucous membrane at the pyloric end of the stomach, and slight inflammation throughout the whole length of the bowel lining. The liver and lungs were congested; the kidneys appeared to be normal. Petechial haemorrhages were seen under the pericardium. Some little time after exposure to air the whole carcase took on a red colour—due, presumably, to the oxidation of the thionol which is one of the products of phenothiazine in the animal body and is responsible for the red coloration of the urine. Portions of tissue taken for sectioning also produced a bright pink coloration in the fixative.

A second calf, 12 weeks old, and weighing about 150 lb., received a dose of 200 grammes on the same date, October 26th; on the 27th it was found to be lying down and refused food, during the following eight days it became increasingly weak and it died on November 5th.

At *post-mortem* examination ulceration of the abomasal mucous membrane was again seen, particularly at the pyloric end, the contents of the rumen were very fluid and there were signs of slight inflammation in the mucous membrane of the first, second and third stomachs. The intestines were also slightly inflamed. The liver was friable and yellowish in colour; the kidneys appeared to be enlarged but did not show pathological changes on macroscopic examination.

A third calf, 5 months old but weak and very small, weighing only 105 lb., was dosed with 85 grammes of phenothiazine in the form of a drench. On the following morning it was found lying down, sweating and showing signs of great distress, the abdomen being distended. As it appeared to be no better in the afternoon it was destroyed. At *post-mortem* examination the mucous membrane of the abomasum was found to be acutely inflamed, particularly at the pyloric end where ulceration had begun. Slight inflammation of the small intestine, extending into the caecum was also observed. The liver and kidneys were normal.

A fourth calf, also 5 months old, but well grown, weighing 273 lb., was treated with 100 grammes in liquid form but showed no untoward results whatsoever; it went on feeding and behaving in a perfectly normal way from the time that the dose was given.

Summary of Observations in Cattle.—Although two experiments—Nos. 10 and 11—gave indications of good results similar to those obtained in sheep, observations on the tolerance of cattle show them to be sensitive to the toxic action of the drug and suggest that a dose of something like two grammes per kilo may prove fatal to a 3 to 5-months-old calf.

It seems probable that the drug will prove less useful in cattle than in other ruminants.

Horses

The remarkably good results obtained in the treatment of horses are recorded in Table VIII, *a*, *b*, and *c*, and represent data which we have been able to collect since September 15th, 1939, when the first trial was carried out.*

The method of procedure has been to omit one or perhaps two feeds in order to increase the animal's appetite and then to offer the powdered drug mixed with a bran mash or with a little oats and treacle when, as a rule, the horse would take it voluntarily.

The method followed in carrying out the faecal examinations was as follows: First, an estimate of the number of eggs per gramme was made by applying the new

*The trials in horses have been carried out with the kind co-operation of the following veterinarians and people associated with thoroughbred studs: J. R. Barker, J. Bell, J. W. Bruford, F. J. Carless, P. Crosfield, K. D. Downham, C. C. Edmunds, J. Macarthur, and E. B. Reynolds.

McMaster technique,† then the faeces were cultured at 26° C. and in eight days time the third-stage larvae separated by means of Baermann's apparatus; these were then differentiated into species and groups of species, and the original egg count divided proportionately.

These trials demonstrate a very remarkable efficiency for all of the strongyloid parasites of the large intestine, the adults at least, being completely eradicated as the result of the administration of a dose of between 30 and 40 grammes.

Trichostrongylus axei, presumably because of its different situation (in the stomach), is more resistant and in several instances appears to have been the only strongyloid parasite to withstand the treatment. *Ascaris* also responds to the treatment but *Anoplocephala,* data concerning which are not given in the table, did not.

Tolerance of Horses.—Horses appear to be very good subjects for treatment with phenothiazine, the large number of trials, data from which are set down in Table VIII, a, b, and c, having been carried out without any definite symptoms of intoxication although in several instances slight inappetence was observed about 24 hours after treatment.

Summary of Observations in Horses.—Phenothiazine at a dose rate of 0·06 gramme to 0·08 gramme per kg. body weight (30 grammes to 40 grammes for a hunter) is 100 per cent. efficient against red-worms. A dose of 20 grammes is also effective but less reliable, but a dose of 10 grammes produces no anthelmintic effect. *Trichostrongylus axei* does not respond well nor do *Anoplocephala* spp. but *Ascaris* is, as a rule, satisfactorily expelled.

Horses appear to tolerate this drug very well indeed, no clear instance of intoxication having been observed.

Effect of Phenothiazine on Eggs and on the Development of Infective Larvae in the Faeces

Examination of faeces from a calf which had received 45 grammes of phenothiazine on the previous day showed all of the eggs (some 1,100 per gramme) to be dead; the contents being opaque and shapeless and showing signs of degeneration.

Observations subsequently made on goats receiving small doses of phenothiazine showed that amounts too small to have any effect upon the adult worms were nevertheless sufficient to prevent the development of the larvae. The smallest dose employed was 0·25 gramme and as a goat passes something like 1,000 grammes of faeces during a day and the excretion of the phenothiazine in the faeces would be spread over three days it is obvious that the amount requisite for the prevention of larval development must be something quite small, presumably in the region of one part of phenothiazine in 8,000 of faeces.

The data from which this conclusion has been drawn are set down in Table IX.

Trials later carried out *in vitro* showed that a mixture of 1:100 or of 1:1,000 of phenothiazine powder in the faeces culture prevented the development of the larvae in a similar way. It was interesting to note, however, in an experiment in which the four treated goats were carrying a particularly heavy infection of *Muellerius,* that no effect whatsoever was produced on the larvae of this genus of lung-worms, living larvae being recovered from the culture in thousands.

†The McMaster egg counting technique has been found, in our hands, to be as accurate as the dilution method previously in use at this Laboratory and is a quicker and more convenient way of working. We have introduced one slight improvement in that the 3 gramme sample of faeces is first mixed with water, centrifugalised and the supernatent cloudy liquid discarded before a 66 per cent. saturated salt solution is added and the count made in the special cell described by Gordon and Whitlock (1939). This preliminary washing not only allows a greater amount of light to make its way through the preparation but permits of the enumeration of the eggs of *Ascaris, Trichuris* and *Fasciola* and of lungworm larvae. These do not float to the top of the two-thirds saturated salt solution that is found to be the most useful medium for the enumeration of strongyloid eggs.

An observation was next made to ascertain at what stage of larval development the action of the drug is most marked. Six 50-gramme cultures were made up for this purpose, half a gramme of phenothiazine being added to each at various stages during the culture period. When larvae were ultimately separated by means of Baermann's apparatus on the eighth day it was found that the drug had exerted its greatest influence on the eggs and early stages of development of the larvae. After the fifth day of development, *i.e.,* when the larvae had reached the infective stage, the drug had taken comparatively little action. Particulars of this observation are shown in Table X.

Action in Vitro.—Solutions of phenothiazine of various strengths were prepared in physiological saline, between 20 and 30 *Trichostrongylus* worms, freshly collected at *post-mortem* examination, being placed in each solution and kept at 37° C.

The results show that within 18 hours the saturated and half saturated solutions had begun to take effect although all of the test worms were not killed until they had been in these solutions for 66 hours. The quarter-saturated solution also appeared to take some effect but test worms in the eighth-saturated solutions behaved in the same way as the controls in physiological saline.

As phenothiazine is described by chemists as "practically insoluble" this result would suggest a very potent anthelmintic action on the part of the very small amount of substance in solution.*

(*For Tables* (*Experimental Data Section*) *see Pages* 640-644.)

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Phenothiazine as an Anthelmintic

DISCUSSION—Mentioning Data reported in Other Contributions to the Symposium†

General Anthelmintic Action.

The extensive observations which are here reported on the anthelmintic action of phenothiazine in farm animals provide ample evidence of the great importance of the discovery of this parasiticide in the annals of helminth control by the use of drugs.

In common with other anthelmintics its mode of action remains something of a mystery, and its addition to the short list of really effective medicinal parasiticides cannot be regarded as the outcome of a scientific understanding of the principles by which their action is governed. The use of phenothiazine as an anthelmintic can be traced back through a series of rational trials to the first observation on its insecticidal properties, made by the workers in the United States Bureau of Chemistry and Soils, who on account of the lack of information at present available on the correlations between chemical structure and parasiticidal action were forced to carry out their investigations by a method of trial and error. As each new anthelmintic substance is found, however, fresh opportunity for study is provided, and it is not improbable that an investigation of some of the peculiar points concerning phenothiazine treatment may help to explain the mode of anthelmintic action.

The most outstanding peculiarity concerns the requirement for a large dose of the drug. Although it is practically insoluble in water we were able to demonstrate a definite parasiticidal action on adult worms *in vitro,* and a very marked toxic action on the

(*Continued on Page* 644.)

*A. Eden of this laboratory has determined the solubility for us as being not greater than one in 50,000.

†"We" in this discussion refers to Taylor and Sanderson. Wherever reference is made to the work of other contributors to the symposium the name is given.

TABLE I (Experiment No. 1.)

Worms recovered at post-mortem *examination from six lambs dosed with 15 grammes of Swales phenothiazine mixture, and from five undosed controls.*

	No. of Lambs.	Stomach.						Small Intestine.								Eggs per Gramme Faeces.	
		Total.	*O. circumcincta.*	*O. trifurcata.*	*T. axei.*	*H. contortus.*	Larvae.	Total.	*T. vitrinus.*	*T. colubriformis.*	*C. curticei.*	*C. oncophora.*	*N. filicollis.*	Larvae.	*Moniezia.*	Before Dosing.	5 Days After Dosing.
Control Lambs	92	55,400	25,853	5,540	9,233	—	14,774	48,318	40,250	1,610	—	—	—	6,440	18	No count made	
	83	26,300	18,410	2,630	5,260	—	—	51,412	30,840	2,570	2,570	2,570	12,550	—	12	6,900	12,800
	84	15,100	11,325	1,510	2,265	—	—	15,500	6,200	3,875	—	—	4,650	775	—	11,500	5,300
	85	19,200	7,642	4,775	6,685	100	—	44,104	39,690	—	2,205	—	—	—	4	10,700	4,000
	90	2,100	2,100	—	—	—	—	13,002	9,750	1,300	650	—	1,300	—	2	1,600	1,900
	Average	23,620	13,066	2,891	4,689	20	2,955	34,467	25,346	1,871	1,081	514	3,700	241	7	7,675	6,000
Treated Lambs	88	—	—	—	—	—	—	1,004	400	—	—	—	—	600	4	4,200	200
	91	—	—	—	—	—	—	5,702	—	5,130	—	570	—	—	2	6,500	200
	89	—	—	—	—	—	—	9,407	2,350	—	470	—	6,500	—	7	8,700	600
	82	—	—	—	—	—	—	19,813	12,870	1,980	990	990	2,970	—	13	15,400	1,900
	87	—	—	—	—	—	—	3,004	2,100	600	—	—	300	—	4	5,600	300
	86	—	—	—	—	—	—	1,600	960	640	—	—	—	—	—	2,800	100
	Average	—	—	—	—	—	—	6,755	3,113	1,391	243	260	1,628	100	5	7,200	550
	Indicated efficiency per cent.	100	100	100	100	100	100	80·4	87·7	25·6	77·7	49·4	56·0	58·0			

TABLE II (Experiment No. 9.) *Showing the effect of small doses of phenothiazine in goats*

No. of Goat.	Grammes of Phenothiazine Given.				Eggs per Gramme of Faeces.										Worms Found in Stomach.				Worms Found in Small Intestine.			Worms Found in Large Intestine.			Eggs per Gramme in Faeces.
	10.4.40.	17.4.40.	22.4.40.	26.4.40.	27.3.40.	11.4.40.	12.4.40.	15.4.40.	17.4.40.	22.4.40.	26.4.40.	30.4.40.	4.5.40.	7.5.40.	*H. contortus.*	*O. circumcincta.*	*O. trifurcata.*	*T. axei.*	*T. vitrinus.*	*T. colubriformis.*	*N. filicollis.*	*T. ovis.*	*O. venulosum.*	*S. ovis.*	
396	[illegible]	[illegible]	4	6	3,800	7,500	7,100	8,200	5,500	7,000	1,100	1,900	2,500	1,400	—	200	200	1,400	2,700	2,340	360	1	24	30	1,400
397	[illegible]	[illegible]	4	6	1,100	1,300	300	600	700	1,400	600	200	500	200	—	—	—	200	1,200	1,200	—	1	8	—	200
425	[illegible]	[illegible]	4	6	2,100	1,500	1,600	2,500	2,300	2,600	3,600	2,000	1,400	1,300	—	400	400	300	4,000	800	—	7	20	—	1,300
430	[illegible]	[illegible]	4	6	1,200	3,400	3,500	2,200	5,700	6,600	1,500	600	200	100	—	100	—	100	500	200	200	10	—	—	100
386	1	1	8	12	300	100	200	300	600	100	0	0	0	0	—	—	—	—	—	—	—	22	2	—	—
418	1	1	8	12	4,400	4,500	5,700	6,900	1,600	1,700	100	100	100	0	—	100	—	—	400	—	—	—	—	—	—
428	1	1	8	12	2,400	4,600	8,000	9,400	7,000	2,400	2,100	3,200	4,300	4,200	100	3,173	—	20,627	11,873	1,827	—	15	—	2	4,200
436	1	1	8	12	2,000	2,300	1,300	3,800	2,500	3,300	800	700	600	500	900	2,000	—	2,700	1,200	1,500	—	48	185	308	541

TABLE III (Experiment No. 2.)

Showing the effect of a 15 gramme dose of phenothiazine administered at the end of an outbreak of parasitic gastritis to a group of 20 lambs many of which had been severely affected

Dates of Dosings and Weighings.	20 Lambs dosed with Phenothiazine.			20 Control Lambs.		
	Average Weight in lb.	Average Increase in Weight.	Egg Count per gramme.	Average Weight in lb.	Average Increase in Weight.	Egg Count per gramme.
13.9.39	61·1		2,400	61·1		2,300
22.9.39	64·2	3·1		63·4	2·3	
29.9.39	65·4	1·2	500	64·4	1·0	1,400
13.10.39	70·8	5·4		68·6	4·2	

For particulars of worm infestation see Table I, the lambs referred to in Tables I and III belonging to the same flock.
Increase in favour of dosed sheep = 2·2 lb. per head in one month.

TABLE IV (Experiment No. 3.)

Showing the effect of a 20 gramme dose of phenothiazine administered towards the end of an outbreak of parasitic gastritis to a group of 28 lambs many of which had been severely affected. Species of Ostertagia *were principally concerned in this outbreak*

Dates of Dosings and Weighings.	28 Lambs dosed with Phenothiazine.			28 Control Lambs.		
	Average Weight in lb.	Average Increase in Weight.	Egg Count per gramme.	Average Weight in lb.	Average Increase in Weight.	Egg Count per gramme.
30.9.39	61·3		5,100	63·4		5,100
21.10.39	74·0	12·7	200	67·5	4·1	2,400
14.11.39	78·3	4·3	200	68·4	0·9	1,400

Increase in favour of dosed sheep in six weeks = 12 lb. per head, or a total of 336 lb.

TABLE V (Experiment No. 4.)

Showing the effect of a 30 gramme dose of phenothiazine administered to lambs two months after the termination of an outbreak of parasitic gastritis, resulting principally from an Ostertagia *infestation*

Dates of Dosing and Weighing.	10 Lambs dosed with 30 grammes Phenothiazine.			20 Control Lambs.		
	Average Weight in lb.	Average Increase in Weight.	Egg Count per gramme.	Average Weight in lb.	Average Increase in Weight.	Egg Count per gramme.
31.10.39	78·0		4,500	84·1		4,500
23.11.39	80·3	2·3	200	84·3	0·2	5,300

Increase in favour of dosed lambs = 2·1 lb. per head in three weeks.

TABLE VI

Showing the effect of small doses of phenothiazine on a mixed infection, principally Haemonchus contortus, *in sheep*

No. of Sheep.	Grammes of Phenothiazine given.				Eggs per gramme of Faeces.							
	19.4.40	23.4.40	27.4.40	1.5.40	12.4.40	20.4.40	23.4.40	27.4.40	1.5.40	6.5.40	10.5.40	15.5.40
1	¼	1	3	5	12,000	16,900	22,900	2,000	800	300	400	300
2	¼	1	3	5	2,600	5,900	4,900	6,300	700	100	700	700
3	¼	1	3	5	800	2,900	2,500	2,800	300	200	400	400
4	¼	1	3	5	500	300	1,300	800	800	1,200	700	400
5	½	2	4	6	7,600	3,900	5,700	7,700	700	100	300	1,000
6	½	2	4	6	2,200	2,400	7,200	1,600	500	600	500	300
7	½	2	4	6	1,000	4,100	3,900	2,100	500	100	200	800
8	½	2	4	6	800	1,500	3,500	1,500	600	200	700	400

TABLE VII

Showing the effect of the repeated administration of small doses of phenothiazine to sheep

Date.	Eggs per Gramme of Faeces in Six Experimental Sheep.					
	2 Gramme Doses of Phenothiazine Daily.		5 Gramme Doses of Phenothiazine Daily.		10 Gramme Doses of Phenothiazine Daily.	
	Sheep 1.	Sheep 2.	Sheep 3.	Sheep 4.	Sheep 5.	Sheep 6.
26.1.40	2,800	700	600	900	7,700	2,100
2.2.40	2,800	200	2,600	100	7,400	500
3.2.40	400	200	1,400	—	2,300	200
5.2.40	300	100	200	—	400	—
6.2.40	100	—	100	—	100	—
7.2.40	100	400	200	—	—	—
8.2.40	100	200	100	—	—	100
9.2.40	100	—	500	—	—	200
10.2.40	—	—	200	—	—	—
12.2.40	700	—	—	—	—	—
13.2.40	100	100	100	—	—	—
14.2.40	200	—	—	—	—	—
15.2.40	400	100	—	—	—	Died
16.2.40	—	—	—	—	—	
17.2.40	—	100	—	—	—	
19.2.40	—	100	—	—	—	
20.2.40	100	100	—	—	—	
21.2.40	—	—	—	—	—	
22.2.40	100	—	—	—	—	
23.2.40	—	—	—	—	—	
24.2.40	—	—	—	—	—	
25.2.40	—	—	—	—	—	
26.2.40	—	—	—	—	—	
27.2.40	—	200	—	—	—	
28.2.40	—	100	—	—	—	
29.2.40	100	100	—	—	—	

TABLE VIIIA

Showing the effect of doses of phenothiazine ranging from 10 grammes to 25 grammes on strongyloid worms in horses

Particulars of Horse.	Dose of Phenothiazine in Grammes.	Egg Count Before Treatment.						Egg Count 2 to 4 Weeks After Treatment.					
		Ascaris.	*Trichonema*, etc.	*S. edentatus.*	*S. equinus.*	*S. vulgaris.*	*T. axei.*	*Ascaris.*	*Trichonema*, etc.	*S. edentatus.*	*S. equinus.*	*S. vulgaris.*	*T. axei.*
	10	—	350	115	5	30	0	0	864	216	0	120	0
	„	—	790	140	20	50	0	0	1,411	136	0	154	0
	„	—	98	80	40	18	0	0	178	12	10	0	0
6-year-old Hunter	„	—	616	341	0	66	77	0	1,064	84	0	28	224
4-year-old „	„	—	803	275	0	11	11	0	1,920	336	0	144	0
11-year-old „	„	—	304	0	0	68	28	0	882	0	0	9	9
5-year-old „	„	—	97	1	0	0	2	0	837	9	0	54	0
9-year-old „	„	—	69	12	0	16	3	0	1,425	0	0	75	0
10-year-old Thoroughbred	„	—	1,392	0	0	208	0	0	255	12	0	21	12
8-year-old „	15	—	336	24	0	240	0	0	648	40	0	112	0
3-year-old „	„	—	372	108	12	696	12	0	40	3	0	57	0
1-year-old „	„	—	528	0	0	624	48	0	0	0	0	24	0
2-year-old „	„	—	462	14	0	224	0	0	0	0	0	+	0
	20	—	600	0	0	0	0	0	1	0	0	0	0
	„	—	400	0	0	0	0	0	100	0	0	0	0
1-year-old „	„	—	679	14	0	7	0	0	+	0	0	0	+
Yearling Hunter ...	„	500	3,485	123	0	492	0	0	0	0	0	1	0
	„	—	1,170	18	0	612	0	0	8	6	0	186	0
3-year-old „	25	—	1,216	32	0	352	0	0	0	80	0	320	0
3-year-old „	„	—	480	450	0	570	0	0	20	40	0	340	0

— = less than 100 per gramme. + = less than 1 per gramme. 0 = absent.

TABLE VIIIB

Showing the effect of a dose of 30 grammes of phenothiazine on strongyloid worms in horses

Particulars of Horse.	Dose of Phenothiazine in Grammes.	Egg Count Before Treatment.						Egg Count 2 to 4 Weeks After Treatment.					
		Ascaris.	*Trichonema*, etc.	*S. edentatus.*	*S. equinus.*	*S. vulgaris.*	*T. axei.*	*Ascaris.*	*Trichonema*, etc.	*S. edentatus.*	*S. equinus.*	*S. vulgaris.*	*T. axei.*
Thoroughbred Foal...	30	200	400	400	0	0	0	0	0	0	0	0	8
"	"	500	300	300	0	0	0	0	0	0	0	0	33
"	"	—	1,600	0	0	0	0	0	11	3	0	0	1
4-year-old Thoroughbred	"	—	252	24	0	0	24	0	3	0	0	0	3
2-year-old " ...	"	—	495	0	0	5	0	0	0	0	0	+	+
2-year-old " ...	"	—	384	12	0	4	0	0	+	0	0	+	0
Yearling	"	100	640	0	0	144	16	2	0	0	0	0	0
Thoroughbred ...	"	—	720	32	0	48	0	0	0	0	0	0	8
" ...	"	200	1,581	85	0	34	0	300	0	0	0	0	0
" ...	"	300	990	33	0	77	0	0	0	0	0	0	0
" ...	"	—	344	28	0	28	0	0	0	0	0	0	0
" ...	"	—	156	87	0	36	21	0	0	0	0	0	1
" ...	"	—	920	0	0	70	10	0	0	0	0	0	2
" ...	"	—	640	0	0	160	0	0	0	0	0	0	2
" ...	"	—	700	0	0	0	0	0	0	0	0	0	0
" ...	"	—	192	4	0	2	2	0	0	0	0	0	5

— = less than 100 per gramme. + = less than 100 per gramme. 0 = absent.

TABLE VIIIC

Showing the effect of doses of 50 and 60 grammes of phenothiazine on strongyloid worms in horses

Particulars of Horse.	Dose of Phenothiazine in Grammes.	Egg Count Before Treatment.						Egg Count 2 to 4 Weeks After Treatment.					
		Ascaris.	*Trichonema*, etc.	*S. edentatus.*	*S. equinus.*	*S. vulgaris.*	*T. axei.*	*Ascaris.*	*Trichonema*, etc.	*S. edentatus.*	*S. equinus.*	*S. vulgaris.*	*T. axei.*
4-year-old Thoroughbred	50	—	500	0	0	0	0	0	+	0	0	+	0
	"	—	1,598	34	0	68	0	0	0	0	0	4	0
7-year-old	60	—	500	0	0	0	0	0	1	0	0	0	0
	"	—	800	0	0	0	0	0	0	0	0	0	0
Cart colt	"	—	546	112	0	21	21	0	0	1	0	0	6
Thoroughbred barren mare	"	—	95	2	0	0	3	0	0	0	0	0	0
" "	"	—	700	0	0	0	0	0	0	0	0	0	0
" "	"	—	8	0	0	0	0	0	0	0	0	0	0
" "	"	—	465	35	0	0	0	0	0	0	0	0	0
" "	"	—	776	8	0	0	16	0	0	0	0	0	200
6-year-old Thoroughbred	"	—	1,064	84	0	28	0	0	0	0	0	0	7
4-year-old "	"	—	1,920	336	0	144	0	0	0	0	0	0	8
11-year-old "	"	—	882	0	0	9	0	0	0	0	0	0	0
5-year-old "	"	—	837	9	0	54	0	0	0	6	0	0	0
9-year-old "	"	—	1,425	0	0	75	0	0	0	1	0	5	0
Thoroughbred ...	"	—	980	0	0	20	0	0	0	0	0	0	2
" ...	"	—	990	0	0	10	0	0	0	0	0	0	0
" ...	"	—	207	48	3	39	3	0	0	0	0	0	2
Debilitated hunter ...	"	—	1,092	60	0	48	0	0	0	0	0	0	0
" " ...	"	—	972	228	0	0	0	0	+	0	0	0	0
" " ...	"	—	1,805	95	0	0	0	0	0	0	0	0	0
" " ...	"	—	658	42	0	0	0	0	0	0	0	0	+
" " ...	"	—	282	12	0	0	6	0	0	0	0	0	4
" " ...	"	—	178	14	0	0	0	0	0	0	0	0	0

— = less than 100 per gramme. + = less than 1 per gramme. 0 = absent.

TABLE IX

Showing the effect of small doses of phenothiazine in preventing the development of third-stage larvae in the faeces of goats

Date.	Dose of Phenothiazine in Grammes.	Goat 388.		Goat 389.		Goat 414.	
		Eggs per Gramme of Faeces.	Larvae per Gramme of Faeces.	Eggs per Gramme of Faeces.	Larvae per Gramme of Faeces.	Eggs per Gramme of Faeces.	Larvae per Gramme of Faeces.
7.3.40	0·25						
8.3.40		1,500	0	200	0	500	0
9.3.40		2,400	11	300	0	600	25
11.3.40	0·75	2,600	54	300	9	400	81
12.3.40		1,300	0	0	0	300	0
13.3.40	1·0	2,800	2	400	6	900	96
14.3.40		1,400	0	500	0	300	0
15.3.40	1·25	1,200	7	200	0	300	0
16.3.40		1,000	0	500	0	400	0
18.3.40	1·5	1,700	34	500	19	400	87
19.3.40		700	0	200	0	100	0
20.3.40	1·75	1,100	0	200	0	300	0
21.3.40		500	0	400	0	500	0
25.3.40		500	2	400	0	200	0
26.3.40		500	86	200	130	300	144
27.3.40		600	51	100	19	400	140
28.3.40		700	170	300	112	700	92
1.4.40		800	124	400	132	600	204

TABLE X

Showing the effect on the development of larvae of a mixture of 1 per cent. of phenothiazine in the faeces added at various stages during the culture period

Date when 1 per cent. Phenothiazine was Mixed with Cultures made 15.12.39.	Number of Trichostrongyloid Larvae Recovered 23.12.39.	Date when 1 per cent. Phenothiazine was Mixed with Cultures made 15.12.39.	Number of Trichostrongyloid Larvae Recovered 23.12.39.
15.12.39	0	19.12.39	30,640
16.12.39	2	20.12.39	53,200
18.12.39	5,680	Control	88,000

eggs and preinfective larval stages of strongyloid worms in faeces, operating down to a dilution of about one part of the drug in 8,000 parts of faeces. (It was interesting to note, however, that *Muellerius* larvae were quite unaffected.) Knipling (1938) obtained similar results in his observations on the control of the hornfly in cattle when he found that the phenothiazine passing through the intestine of cattle for three days after dosing was sufficient to inhibit the development of hornfly larvae in the faeces.

These observations are suggestive of an extremely potent action of this drug since the actual amount in solution must be very small indeed, and it is surprising to find that rather large doses are requisite for full anthelmintic action. Swales (1939) considered it necessary to give 20 or 30 grammes to a sheep and Swanson *et al.* (1940) gave up to 30 grammes to a pig. Although our observations indicate the adequacy of a smaller dose it is nevertheless much greater than the tests *in vitro* would seem to indicate. Our results suggest that a dose of 5 grammes produces a good anthelmintic effect in sheep, and that 10 grammes approaches to the maximum anthelmintic effect. Ten grammes to a horse was clearly inadequate but 20 grammes, in some instances, proved to be 100 per cent. efficient, although in others its action was much less marked : 30 grammes however produced the maximum result in almost every instance and it may be concluded from our results that for ordinary purposes, 10 grammes (0·3 grammes per kilo) is adequate for a sheep and 30 grammes (0·06 grammes per kilo) for a horse.

An interesting observation in connection with dosage was made at the Zoological Gardens, London, by G. M. Vevers who, in a private communication, reported the expulsion of large numbers of *Enterobius* from a gorilla as the result of the administration of only 0·5 grammes of phenothiazine.

There is, therefore, seen to be something unusual about the anthelmintic action of this drug in that the dose generally required, having regard to the insolubility of the drug, seems to be unnecessarily large. In an endeavour to explain this peculiarity we considered the possibility of the formation within the animal body, of some second substance, of much greater anthelmintic potency than that of phenothiazine, and for this purpose we administered 30 grammes to one goat, collected the faeces on the second day afterwards and administered 30 grammes of the phenothiazine-containing faeces to a second goat heavily infected with parasitic worms. A filtrate of a watery solution of another 30 grammes of the same faeces was administered to a third goat, also heavily infected with parasitic

worms. Observations on the egg output of the two goats that received the "medicated" faeces failed, however, to reveal any effect on the parasitic worms.

Following this observation we carried out two trials with oxidation products of phenothiazine produced within the animal body. The first of these was thionol* which is the red dye that causes the red coloration of the urine in animals treated with phenothiazine and is the oxidation product of leucothionol which, after exposure of small portions of tissue to the air, is seen to be present in almost every part of the body of an animal that has received a large dose of phenothiazine. These substances form the reversible oxidation-reduction system thionol—leucothionol, similar to that of methylene blue—leucomethylene blue, well known to workers on clean milk. The second substance was phenothiazone which according to Gersdorff and Claborn (1938) is extremely toxic to goldfish.

Both of these substances were tested in doses of 0·25 grammes and 2 grammes in goats heavily infected with parasitic worms but without producing any anthelmintic effect whatsoever.

Nothing, therefore, was done to elucidate the reason for the necessity of giving much more phenothiazine than is required to produce a saturated solution in the contents of the intestinal tract in order to produce anthelmintic action,† but it seems not unlikely that some factor of importance for the understanding of the action of phenothiazine, and, possibly for the understanding of anthelmintic action in general, lies hidden in this one particular problem.

Specificity of Anthelmintic Action.

Our own results show that phenothiazine is particularly lethal to strongyloid worms,‡ its most pronounced and certain action being exerted on those in the large intestine of the horse, where, in adequate dosage, it can be relied upon to eradicate all of the adult forms. The species of *Strongylus*, however, appear to be slightly more resistant than are the smaller "red-worms," *S. vulgaris* being the most resistant of all.

Second only in efficiency is its action on the trichostrongylid worms in the fourth stomach of sheep where, in adequate dosage, it has proved to be 100 per cent. efficient on several occasions; this high efficiency is, however, less reliable than on the red-worms in horses. Species of *Ostertagia* respond particularly well, *Haemonchus* appears to be less sensitive and *Trichostrongylus* and *Cooperia* occupy an intermediate position in this respect.

One interesting point which came to our notice was the very good action of the drug on *Trichostrongylus axei* in the fourth stomach of sheep—100 per cent. frequently being removed—and its comparative lack of action on the same species when present in the stomach of the horse.

The action of the drug on worms in the small intestine of sheep is less pronounced than on those in the fourth stomach but is, nevertheless, better than that of any previously known anthelmintic. Apart from *Moniezia*, on which there is no action, *Nematodirus* appears to be the most resistant, but other species of trichostrongylid parasites in the small intestine may be regarded as giving a satisfactory response.

The results clearly show that there is no action upon *Fasciola*, nor upon *Anoplocephala*.

Action on ascarids is interesting in that it appears to be very good in the horse, moderately good in the pig and almost completely lacking in the dog, as shown by Montgomerie's results. This comparative response of ascarids to phenothiazine in these three kinds of hosts differs from their response to carbon tetrachloride as reported by Hall who found this drug to be more efficient against *Toxocara* and *Toxascaris* in the dog than against *Ascaris* in the horse.

Anthelmintic Effect on the Host.

The beneficial effect of treatment with phenothiazine has been very clearly demonstrated in some of the weighing experiments in which great gains have been observed as a result of the anthelmintic action of the drug. The most striking is described in *experiment 3* in which one 20 gramme dose to each of a group of lambs resulted in the production of 336 lb. of mutton.

Observations carried out by McEwen and Taylor (to be reported later) and by McEwen alone on the Romney Marshes show significant gains in phenothiazine-treated sheep, over and above gains made by similar sheep treated with a mixture of nicotine sulphate and copper sulphate. A difference of 9 lb. per head among a group of 27 lambs was noted in one instance.

The results obtained by J. W. Ironside and K. D. Downham (reported in this paper) in lightly infected flocks are also interesting, showing a slight gain in favour of the treated groups. The trials were, however, not sufficiently extensive to establish this point and the result obtained by S. J. Menzies (also reported here) in comparing phenothiazine with copper sulphate suggests that the effect of copper sulphate may be equally good in instances of slight infestation. On account of the inadequacy of data, however, this point cannot be regarded as certain.

Very good results have been observed wherever it has been tried in horses.

The effect in goats and in cattle has also been very good, apart from the toxic action that has been observed in some instances.

Tolerance and Toxic Action.

Domestic animals in general appear to be extraordinarily tolerant to this drug and there is usually found to be an enormous difference between the anthelmintic dose and the toxic dose. Two sheep and one goat were actually dosed with 80 times an effective anthelmintic dose without any signs of intoxication being produced. Horses appear to be only slightly less tolerant, Lapage, as reported in this symposium, having given as much as 500 grammes without producing marked symptoms, and a repeat dose of the same amount without causing a fatal intoxication; further data given by him, however, strongly suggest that 1,000 grammes produced a fatal result, although lesions found on *post-mortem* examination suggested that other pathological conditions may have been

*The thionol and phenothiazone was kindly prepared for our use by Dr. Sexton of the Imperial Chemical Industries Laboratories at Blackley.

†The theory on which we are working at the present time is that it is necessary to maintain a saturated or nearly saturated solution of phenothiazine in the intestine for some considerable time in order to secure anthelmintic action and that to insure against the exhaustion of the reservoir of phenothiazine in the rumen, or in the large intestine (in equines) it is necessary to give a large dose. *In vitro* observations appear to support this view.

‡An interesting exception has been mentioned by Manson-Bahr, who, in a private communication, reported having found phenothiazine to be relatively ineffective against *Ancyclostoma* although very effective against some other worms in the human being.

involved in the cause of death. Cattle, on the other hand, appear to be more sensitive to the toxic action of phenothiazine, 85 grammes having produced a fatal intoxication in a 105 lb. calf. The observations that we have been able to make concerning the use of the drug in cattle are few, but even in these animals the difference between the anthelmintic and the toxic dose appears to be considerably greater than it is with most, if not all other efficient anthelmintics.

Our observations have, however, revealed evidence of individual idiosyncrasy, or possibly of some special susceptibility associated with diet, so that we cannot yet write with certainty on the general safety of the larger doses. Our experience with goats provides an example of this point in that doses of 20 grammes and 30 grammes produced decided symptoms of intoxication at one time (shortly after the arrival of the animals at the Laboratory) and at a later date amounts as great as 400 grammes failed to produce any signs of even the slightest indisposition.

Some evidence of this occasional intoxication has also been seen in horses, slight constitutional disturbance having been shown on a few occasions, in the form of dullness and inappetence lasting for about 24 hours after the administration of the dose.

Observations made to determine the toxic dose in rabbits showed that a single dose of 6 grammes causes more or less marked constitutional disturbance and that 10 grammes is fatal, representing a toxic dose of 4 grammes per kilo.

The effect of repeated daily doses proved to be more marked; one rabbit died after only four consecutive daily doses of 2 grammes, another after seven daily doses of 5 grammes, a third after 17 daily doses of 1 gramme and a fourth was still surviving and showed little sign of intoxication after 28 daily doses of 0·5 grammes. The toxic repeated daily dose is therefore seen to lie somewhere between 0·05 and 0·1 gramme per kilo.

The principal lesion seen on *post-mortem* examination was that of acute gastritis, the condition being less acute, and progressing to ulceration confined to the pyloric end of the stomach, in the lower doses. In one or two instances, the small intestine was slightly inflamed, the liver sometimes showed signs of fatty degeneration, and the kidneys were sometimes pale in colour and enlarged.*

Further evidence of the greater toxicity of the repeated small doses over one large one was also obtained in *experiment No. 8* in which daily doses of only 10 grammes killed one sheep and caused a relatively severe constitutional disturbance in a second one. A similar result was obtained by Lapage (reported elsewhere in this symposium) who found repeated doses of comparatively small amounts of phenothiazine to be markedly toxic for pigs. Manson-Bahr, in a private communication to us, has reported that no toxic symptoms were noted in a human patient after a thrice-repeated daily dose of 8 grammes, the anthelmintic effect of which was very satisfactory.†

*We have not yet had the opportunity of examining this and other material microscopically. Eddy *et al.* (1937), however, failed to find any injury to tissue after 295 consecutive daily doses to rats although the rats became stunted if the dose was sufficiently high.

†Manson-Bahr gave single doses of 30-40 grammes without ill effect except in one instance, when a 40-gramme dose produced sickness.

Administration and Dosage.

One great advantage of this drug is its comparative tastelessness, so that animals will take it voluntarily mixed with the food, a point which is of particular importance in the treatment of the horse and is likely to add considerably to the extent to which phenothiazine will be generally employed. Although the suspicions of a well-fed animal, on being presented with a medicated feed, may be aroused to such an extent that he will refuse it, a fast of a few hours' duration usually overcomes the disinclination and the feed, which should be made as tempting as possible, is taken without further difficulty.

This method may also be employed in pigs, although Lapage points out elsewhere in this symposium that by mixing the drug with the pigs' food certain members of a group, which are more hungry, or less sensitive to the slight taste of phenothiazine, may get much more than the calculated dose and their companions much less. The method may also be used in the treatment of sheep, and the occasional medication of dry feed in this way is one of the possibilities for carrying out periodic dosing that is worthy of serious consideration. The results of *experiment No. 8* suggest that a dose of 2 grammes may be adequate for this purpose, although 5 grammes is better.

During the early part of our work it was feared that the bulky nature of phenothiazine, and the large size of the dose that was thought to be necessary would have a serious reaction on its general usefulness in sheep. In co-operation with Imperial Chemical Industries, however, two preparations have been made, a suspension containing about 40 per cent. by weight of phenothiazine, and a tablet, containing 5 grammes of phenothiazine along with a little excipient and a substance that brings about the rapid disintegration of the mass when placed in water, these have proved very good indeed.

Every opportunity has been taken to have the two methods of administration (in liquid and in tablet form) tried out by various people who have been using the drug in sheep, and opinion on their relative merits has been almost equally divided. The tablets are given by means of a rubber-ended balling gun and in our experience are to be preferred over the administration of a liquid where the dose to be administered is not a large one. On one occasion we were able to give a dose of 10 grammes (two tablets) to each of 120 lambs in only 45 minutes, without undue haste. Taking into consideration the greater safety of the tablet over the liquid method we are of the opinion that the tablet method is the better, although on account of the necessity of using a special balling gun the liquid may prove the more generally useful preparation.

Cattle can easily be treated by the administration of a liquid or of a draught made from tablets allowed to disintegrate in water or gruel.

General Usefulness.

The general advantages of this new anthelmintic may be listed as follows: (1) very high efficiency for certain parasites, (2) remarkable lack of toxicity, (3) lack of taste, (4) cheapness, (5) no previous preparation being required, (6) no subsequent purgation required. Against advantages the following two disadvantages only can be set: (1) its bulky nature, and (2) the appearance of the red dye thionol in the urine for some

three days after the administration of phenothiazine.*

The production of thionol in the urine is the only one of these points that calls for mention here, the others having been dealt with. It is, of course, always advisable to warn the owner of the treated animals about the appearance of this dye in the urine as it may easily be mistaken for blood and cause alarm where the warning has not been given; apart from this, however, the consequent staining of the wool may be regarded by sheep farmers as a distinct drawback to the general use of phenothiazine, as thionol is a very fast dye and the stain is likely to remain on the wool for some time. As yet no suggestions have been made as to how this objection may be overcome.

There seems to be little doubt that phenothiazine will come into general use for the control of parasitic gastritis in sheep for which it has considerable advantages over any other known anthelmintic; and it is felt that further trials will establish its usefulness for the same disease in cattle, in which animals parasitic gastritis is still without a satisfactory treatment. Australian and American workers have demonstrated its usefulness for the expulsion of oesophagostomes from sheep and some data collected by McEwen and Taylor but not published here, have shown a marked action on *Chabertia*. Its greatest use may, however, prove to be in the treatment of strongylosis in equines, where it can be relied upon to exert a 100 per cent. efficiency. If the safety of this treatment is also taken into consideration there seems to be every reason for its frequent and regular employment in horses and it is by no means too extravagant to suppose that by regular dosings every two or three weeks it may prove possible to eradicate the infestation from certain environments, a procedure which could not previously have been contemplated with hope of success.

Summary

Phenothiazine is shown by the tests reported in this symposium, on some 150 horses, to be remarkably efficient against the strongyloid parasites in the large bowel of these animals, a dose of 30 to 40 grammes proving to have an absolute efficiency of 100 per cent. for adult worms.

The ease of administration and the safety of the drug are such that the eradication of red-worms from well-managed studs now appears to be a possibility.

Phenothiazine is also remarkably efficient against the stomach worms associated with parasitic gastritis in ruminants, as demonstrated by the several observations involving some 300 to 400 sheep, 70 to 80 goats and a dozen cattle. In the small intestine of these animals it is less efficient but removes about 80 per cent. of the trichostrongylid parasites there, with the exception of *Nematodirus*, on which it exerts very little action.

There is no action against *Fasciola* nor against the anoplocephaline cestodes *Moniezia* and *Anoplocephala*.

Ten grammes appears to be an adequate dose in sheep or goats although doses of 20 to 30 grammes are more likely to produce the maximum effect.

Cattle respond well but are much less tolerant of the drug than are sheep or horses.

Experiments on pigs and dogs have been few but it is clear that although the drug acts well on ascarids in the horse its action against these parasites is uncertain in the pig and is absent in the dog.

The anthelmintic effect noted on sheep that have been more or less heavily infested with stomach worms has been extraordinarily good and, where comparisons have been made, has generally been superior to that of copper sulphate and nicotine sulphate.

The tolerance of sheep and goats is very high, 400 grammes causing no ill effect: horses withstand up to 17 times the anthelmintic dose.

Some evidence of idiosyncrasy has been observed in that a group of goats showed some sensitivity to the drug on one occasion and on a later occasion proved to be very resistant to toxic action.

Repeated small doses are considerably more toxic than are occasional larger doses, the minimum toxic single dose being about forty times as great as the minimum toxic dose when repeated daily.

The tasteless character of phenothiazine is a great advantage in that horses will take it voluntarily in the food; pigs and sheep may also be dosed in this way.

* The danger should also be kept in mind of the coloration of the carcase, and particularly the kidneys with thionol as the result of giving a large dose to lambs up to three days before slaughter.

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EXPERIMENTS ON THE ANTHELMINTIC ACTION OF PHENOTHIAZINE

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The experiments described below were begun in October, 1939, and formed part of the field trials which, as Dr. Taylor explains elsewhere in this symposium, were instituted by the Agricultural Research Council. They were planned with the advice and practical assistance of Professor Dalling, F. Blakemore, M.R.C.V.S. D.V.S.M., F. Day, F.R.C.V.S., and J. A. J. Venn, M.R.C.V.S., D.V.S.M. Professor Keilin, Director of the Molteno Institute, University of Cambridge, made the spectroscopic examinations of the blood of some of the horses. The egg and differential worm counts would not have been possible without the skilled help of H. E. Bowman. The phenothiazine used was supplied by the Agricultural Research Council and was therefore part of the stock which was also supplied to the other contributors to this symposium. Most of the contributors judged the effect of phenothiazine by egg counts and periodical weighings of the animals treated and the writer also followed this practice, except that he did a series of egg counts before the dose was given and took the average, in every instance, between the counts done on two different portions of the same sample of faeces, these two counts being done by different observers. These two counts on the same sample of faeces often differed very considerably, so that the precaution of taking the average of two was amply justified. It was unfortunately not possible to supplement the egg counts and weighings with autopsies, histological examinations of organs removed, especially of the kidney and the liver, and by examinations of the blood (although the blood of some of the horses was examined), but these further examinations are being done on animals being used for additional experiments now in progress. The object of these additional experiments is to gather further information about (1) the relative efficiencies of copper sulphate alone, copper sulphate and nicotine, phenothiazine suspended in liquics and tablets of phenothiazine; (2) the effect of phenothiazine on the host; (3) the greater or less effect of phenothiazine on particular species of nematodes. There is some evidence in the literature and in private communications to the writer, which suggests that phenothiazine acts most powerfully on nematodes living in the abomasum and in the lower parts of the bowel, and that it has less effect on nematodes living in the duodenum and the upper part of the small intestine. This evidence is not in any way conclusive, but it seems to the writer that this question should be investigated further. The study of it could well be combined with a study of (4) the effects, if any, of the environment of intestinal nematodes on phenothiazine and (5) the mode of action of phenothiazine, about which we know nothing at all. Taylor records in this symposium that phenothiazine, in amounts far too small to have any anthelmintic action in a host animal, will inhibit the development of eggs and early larvae, although they do not affect the infective larvae. Such *in vitro* observations suggest a direct action of the drug. On the other hand, there is evidence which suggests that the action of phenothiazine is more pronounced in ruminant hosts, in which the drug has to pass through the rumen and other oesophageal chambers of these animals, than it is in omnivorous hosts such as the pig and the dog. It is possible that the intestinal contents of ruminants allow the drug freer access to the nematodes than the pastier faeces of omnivora do, but other factors probably operate as well. Swanson, Harwood and Connelly (1940) (*J. Amer. vet. med. Ass.* **96.** 333-338) found that phenothiazine was as effective as oil of chenopodium for the removal of ascarids from mature pigs and suggest that the ascaricidal principle of phenothiazine may be "activated by the substances excreted by those worms." They thought it was more effective when the infestations were heavy than when they were lighter. On the other hand, Singer and Baker (1940) (*Cornell Vet.* **30.** 375-382) found that phenothiazine was more effective against lighter nematode infestations of sheep than against heavier ones. Observations like these do, nevertheless, justify the question, which is also raised by other points in the literature: Is phenothiazine inactive as an anthelmintic until it is chemically changed in the gut, so that its action is greater on species living in the lower part of the alimentary canal? There is urgent need for the investigation of this and collateral questions. Associated with them is the problem of why it is necessary, as all workers agree that it is, to give so much phenothiazine, in order to produce an adequate anthelmintic effect, that a great deal of it is passed out again in the faeces apparently unchanged. This is a waste that might be avoided if we knew how phenothiazine acts on a nematode; we might then be able to use a modified form of it, or a derivative of it, which would be more potent and perhaps effective for all nematodes.

TECHNIQUE.—Differential worm counts were made by Taylor's technique (1934.) (*Vet. Rec.* **14.** 474-475).

Egg counts were done by taking 3 grammes of faeces from the animal, either with the finger, or as they were passed, and emulsifying these in 45 c.c. water; 0·15 c.c. of this emulsion was then taken with a pipette and the eggs in this amount counted. Multiplication by 100 gave the number of eggs per gramme.

Wherever possible two counts, made by different observers (Lapage and Bowman), were made from different portions of each sample of faeces and the average of these was taken. Frequently these two counts differed widely. Sometimes one was negative, while the others showed as many as 700 e.p.g. or there were variations as wide as 7,500 and 200 e.p.g. in different portions of the same sample of faeces. It was evident, therefore, that the average of the two counts did not accurately represent the egg content of the faecal samples, but this kind of error is common to all the egg counts made and will not surprise helminthologists. In some experiments composite egg counts of mixed samples from individual animals were made, because it was not possible to do egg counts on each individual animal. Some of the disadvantages of composite egg counts are discussed below.

Swanson, Harwood and Connelly (1940) (*J. Amer. vet. med. Ass.* **96.** 333-338) who studied the action of phenothiazine on *Ascaris* in pigs, used two kinds of phenothiazine, namely, "conditioned" phenothiazine, containing a dispersal agent to render it suitable for use as an insecticidal spray and

"recrystallised" phenothiazine, which was more effective than the "conditioned" product. The writer is informed by Imperial Chemical Industries, who supplied to the Agricultural Research Council the phenothiazine used by the writer, that their phenothiazine, being a distilled product, can be regarded as being as pure as the recrystallised product used by Swanson, Harwood and Connelly.

SHEEP AND LAMBS

1.—Experiment on Two Lambs and One Ewe

These three animals were kept indoors and in the same box throughout the experiment. There was therefore the possibility that self- and cross-infestation could occur. Egg counts were done daily on all three animals for ten days before the phenothiazine was given and, with the exception of a few days, for three months after the dose. The ewe was not dosed and constituted a control.

On 2.11.39 the two lambs, called Marked and Unmarked respectively, were dosed with the tablets of phenothiazine first issued by Imperial Chemical Industries, namely, the 1 gramme tablets, each containing 1 gramme phenothiazine, six of these being enclosed in each gelatine capsule. Each tablet also contained some phenolphthalein and also some tartaric acid and sodium bicarbonate, the two latter ingredients being included to ensure the breakdown of the tablet in the stomach.

On 10.11.39 the Marked lamb, weighing 74 lb., was given four capsules containing a total dose of 24 grammes of phenothiazine (about 0·3 gramme per lb. body weight). On the same date the Unmarked lamb, weighing 89 lb., was also given a total dose of 24 grammes in four gelatine capsules (about 0·27 gramme per lb. body weight).

The effect of these doses on these two lambs was, in both cases, immediate. The day after the dose, the egg count of the Marked Lamb had dropped from a mean of 7,400 to a mean of 1,700. Three days after the dose the mean egg count was 200 e.p.g. and it remained at or near this figure until 56 days after the dose. An attempt was then made to remove the remaining few worms, which were producing a mean egg count at that time of about 200 e.p.g., by giving on 5.1.40, 7 grammes phenothiazine in the form of the same tablets as those that had been given before. This did not lower the egg count. On 10.1.40 a further six tablets (6 grammes) were given, but the egg count was still not appreciably affected. On 18.1.40 and 19.1.40, 12 and 13 days respectively after the second dose, successive doses of 6 grammes of the same tablets were given and the egg count dropped to a mean of 100 e.p.g. Successive doses of 6 grammes of the same tablets were repeated on 25.1.40 and 26.1.40 and the egg count was negative for the next three days, showing a mean of 100 e.p.g. again on the fourth day. Three successive daily doses of 6 grammes of the same tablets were then given on 31.1.40, 1.2.40 and 2.2.40 but, with the exception of a negative egg count on the day after the last of these three doses, no lasting effect on the egg count was noted. No further doses were therefore given. The egg counts remained at a mean of 100 for a further 14 days after the last dose, when the egg counts were discontinued. The animal was, however, kept in the box with the Unmarked Lamb until 8.4.40. On 7.4.40 and 8.4.40 its egg count was 0 and 100 respectively.

The history of the Unmarked Lamb was similar. After the initial dose of 0·27 gramme per lb. body weight (24 grammes) its egg count dropped from a mean of 3,850 e.p.g. to a mean of 550 e.p.g. It remained slightly higher than that of the Marked Lamb. On 6.1.40, 57 days after the initial dose, an attempt to remove its remaining worms was made by giving it in water as a drench 9 grammes of phenothiazine powder. Two days after this dose the egg count had dropped from a mean of 500 e.p.g. to 0. The next day (9.1.40) it had risen again to 50 e.p.g. and remained at this level till 15.1.40, when it was 200 e.p.g. On 17.1.40 it was 350 e.p.g. On 19.1.40 and 20.1.40 two successive doses of 9 grammes each were given in the form of the 1 gramme tablets in gelatine capsules. The day after the second of these doses the egg count was 0 and it remained so until 25.1.40. On this date and on 26.1.40, two further doses of 9 grammes of the same tablets were given and the egg count remained at 0 until 31.1.40, when it was 100. On 31.1.40 and 1.2.40 and 2.2.40, three successive doses of 9 grammes each of the same tablets were given. From 3.2.40 to 7.2.40 the egg count remained at 0, but was at 100 e.p.g. on 7.2.40. It remained at this level until 16.2.40 when the egg counts were discontinued until 8.4.40 when the count was 0 again, although this lamb had been in the same box with the Marked Lamb, which still had an egg count of 50 to 100 e.p.g.

The undosed ewe had a mean egg count on the first three days of the experiment of 1,350, 2,700 and 1,800 respectively, but by the fifth day it had fallen, without dosing, to 600 and thereafter fluctuated between 400 and 800 e.p.g. until 7.12.39, when it was killed off by mistake. It did not therefore provide a very satisfactory control. The fall in its egg count without dosing is, however, a point to be noted, because this frequently happens in all kinds of animals and must be considered when the egg count is used as a criterion of the effect of any anthelmintic.

The conclusion drawn from this experiment was that a dose of about 0·3 gramme per lb. body weight removed most of the worms of a light infestation, but that a few remained, which it was difficult to remove with phenothiazine, perhaps because the animals were confined in a box and probably self- and cross-infestation were occurring all the time. Animals in the field would be subject to much heavier infestations after dosing, so that it would be even more difficult, if not impossible, to reduce their egg counts to 0 and to maintain it so. The reduction of the egg counts to 0 for three or four days was not regarded as significant, because egg counts are notoriously fallible as evidence of the degree of an infestation. In any event, the failure to produce a negative egg count over long periods may carry with it the advantage that the retention of some worms by an animal helps to maintain its resistance to further infestation. On the other hand, Gordon (1939) (*Austral. Vet. J.* 15. 118-120) has pointed out that in a sheep harbouring, say 8,000 *Haemonchus contortus*, half of which may be females each producing 5,000 eggs per 24 hours, a 90 per cent. reduction of the worm burden still leaves 800 worms, 400 of which can be calculated as being females, so that this sheep will still be voiding 2,000,000 eggs in 24 hours—a considerable daily infestation of the pasture if it is multiplied by a number of sheep in a flock.

2.—Experiments on Flocks in the Field

A. Examination of two lambs sent in to the Institute from a farm in Norfolk showed that one contained 3,600 *Ostertagia* in the abomasum and 6,400 *Nematodirus* in the intestine, and the other 35,000 *Ostertagia* in the abomasum and no worms in the small intestine. This flock was regarded as suitable for dosing and experiments.

The owner agreed that 50 animals (ewes and lambs) should be dosed with phenothiazine and 50 with copper sulphate (without nicotine) to compare the effects of these two anthelmintics, the remainder of the flock being dosed with copper sulphate without nicotine. The two lots of 50 ewes and lambs (Groups 1 and 2) were all marked by clipping the ears and each animal was weighed separately on a weighbridge before the dose was given. A faecal sample was taken from the rectum of each animal when the dose was given and these samples were mixed to provide composite samples for each of the two groups. Each of the lambs and ewes in Group 1 was given 5 grammes of phenothiazine in tablet form and each in Group 2 was given 2 oz. of a 1 per cent. solution of copper sulphate without nicotine. On the 10th, 20th and 30th days after the dose each lamb was again weighed on the same weighbridge and a faecal sample was taken from the rectum of each to provide a composite egg count for each of the two groups. The average weight of Group 1 was 53·8 lb. and that of Group 2 54·8 lb.

For the first 20 days the animals were folded on sainfoin and during the first ten days only they all received extra corn rations. For the final ten days they were moved from the sainfoin to tares, the sainfoin having become by then so much woodier in the hot, dry weather that the farmer considered this change advisable.

The following tables show the individual weights of the lambs, the total weights of each group and the egg counts on the composite faecal samples from each group.

Table I

Group 1. *Nos.* 1-50. *Weights stated in lb. Avoirdupois.*

No.	Initial Weight 24.5.40 Before Dose of 5 Grammes Phenothiazine.	Weight 3.6.40.	Weight 13.6.40.	Weight 24.6.40.
1	57	68	71	79
2	48	56	64	67
3	52	60	70	82
4	*53	57	62	71
5	64	70	65	85
6	65	74	73	86
7	63	74	80	86
8	31	34	38	46
9	*60	67	69	77
10	49	56	62	65
11	60	66	72	80
12	57	68	69	79
13	*53	64	71	81
14	68	76	82	90
15	48	56	60	65
16	67	76	83	88
17	*46	58	62	70
18	46	54	60	66
19	40	46	53	58
20	(22)	24	22	22
21	58	71	74	77
22	27	36	40	47
23	*48	58	64	71
24	52	60	66	71
25	66	76	84	87
26	*57	64	72	82
27	(32)	37	38	44
28	64	68	74	76
29	53	60	65	69
30	63	69	74	77
31	63	70	73	80
32	73	82	90	94
33	73	81	84	85
34	54	64	72	77
35	*57	68	75	69
36	58	63	72	82
37	63	76	82	87
38	55	60	66	71
39	45	53	58	61
40	59	66	72	76
41	48	56	60	64
42	60	70	74	82
43	55	64	70	74
44	45	58	66	73
45	51	58	64	71
46	55	62	64	70
47	47	57	56	70
48	55	68	73	79
49	50	60	66	70
50	58	68	64	73

Group 2. *Nos.* 51-100. *Weights stated in lb. Avoirdupois.*

No.	Initial Weight Before Dose of 2 oz. of 1 per cent. Copper Sulphate.	Weight 3.6.40.	Weight 13.6.40.	Weight 24.6.40.
51	58	66	75	82
52	77	93	95	100
53	57	70	76	85
54	53	60	66	75
55	51	56	52	54
56	50	54	56	64
57	37	44	52	58
58	51	58	62	65
59	*53	63	68	76
60	42	50	55	65
61	63	64	70	77
62	70	84	90	91
63	53	58	60	70
64	22	28	30	36
65	50	54	60	64
66	66	72	79	84
67	76	85	92	101
68	50	56	66	73
69	13	16	18	20
70	*64	76	78	89
71	51	62	65	72
72	46	50	57	61
73	*45	55	63	70
74	53	64	76	82
75	49	58	63	65
76	50	57	62	66
77	66	78	85	90
78	57	64	73	78
79	53	60	61	64
80	58	66	64	70
81	54	63	66	76
82	63	70	80	87
83	30	34	38	40
84	60	70	70	74
85	60	71	78	89
86	*44	50	59	68

No.	Initial Weight Before Dose of 2 oz. of 1 per cent. Copper Sulphate.	Weight 3.6.40.	Weight 13.6.40.	Weight 24.6.40.
87	*50	58	66	72
88	*50	58	65	71
89	59	67	64	80
90	73	86	90	96
91	52	60	67	73
92	56	66	73	82
93	51	56	64	67
94	71	80	90	92
95	50	60	68	76
96	61	70	76	87
97	54	60	60	63
98	54	60	64	64
99	76	88	96	100
100	56	64	68	73

It has been suggested (Singer and Baker. (1940.) *Cornell Vet.* **30.** 375-382 and others) that *Nematodirus* is one of the nematodes (*Trichuris* and *Ancylostoma duodenale* may be others) which are comparatively little affected by phenothiazine, but the writer has as yet seen no evidence in favour of this view.

B. Experiment A was repeated on a group of ewes and lambs belonging to this Institute, but the egg counts on the composite faecal samples taken before dosing were low, so that little information was expected from this experiment about the relative efficiencies of phenothiazine and copper sulphate. Further, accidental obliteration of some of the markings prevented the keeping of an accurate record of the weight of individual animals. The two groups A and B were kept separate, grazing on different fields about a mile apart.

TABLE II

Total Weights in lb. Avoirdupois

	Group 1. Nos. 1-50. Given 5 Grammes Phenothiazine.			Group 2. Nos. 51-100. Given 2 oz. of 1 per cent. Copper Sulphate.		
	Total Weight.	Increase.	Eggs per Gramme Average of 2 Counts.	Total Weight.	Increase.	Eggs per Gramme Average of 2 Counts.
24.5.40	2,693		1,050	2,708		2,150
3.6.40	3,107	414 Average 8·3	150	3,012	304 Average 6·08	400
13.6.40	3,440	333 Average 6·6	50	3,369	357 Average 7·1	300
24.6.40	3,642	302 Average 6·04	100	3,677	308 Average 6·1	250

It will be seen that the weight increases of individual lambs differed considerably, and that some of the animals at times lost a few pounds in the intervals of ten days. The main fact emerging from the experiment is that there was no significant difference in the progress of the weight increase in the two groups. The slight advantage on the 20th day in favour of the group given copper sulphate and its disappearance by the 30th day should be noted here, in view of the results of the next two experiments. It could be argued that the dose of phenothiazine that was given was small, a normal therapeutic dose being 10 to 30 grammes. Yet the egg count of Group 1 was reduced by this small dose in about the same proportion as the reduction of the higher egg count of Group 2 by copper sulphate. It could equally well be argued that, in spite of the higher egg count of Group 2, about twice as high as that of Group 1, the copper sulphate enabled this group to maintain a weight increase equivalent to that of Group 1 given a small dose of phenothiazine. The experiment does not tell us whether, if the dose of phenothiazine had been higher, Group 1 would have shown a markedly greater increase of weight than that attained by Group 2. Another experiment, now in progress, may help to answer this question. Meanwhile, this experiment shows that even 5 grammes of phenothiazine has a significant effect on a comparatively heavy infestation with *Haemonchus*, *Ostertagia* and *Nematodirus*.

The following table (*see next page*) gives the relevant data about these animals. It shows that the weight increase during the 23 days following the dose was small. Some animals, like some of those in experiment A, lost a few pounds. Both copper sulphate and phenothiazine reduced the egg count of the ewes to 0, while the egg counts of the lambs were not appreciably affected by either anthelmintic.

It will be seen that in this experiment, unsatisfactory though it was, there was, 23 days after the dose, a slight advantage in weight increase in favour of the group given copper sulphate. In experiment A there was a similar advantage, 20 days after the dose, in favour of the group given copper sulphate. By the 30th day this had disappeared. In the experiment next to be described, the group given phenothiazine attained, by the 30th day, a total weight approaching twice that attained by the group given copper sulphate and nicotine.

C. One hundred lambs, three to four months old, were included in this experiment. On 5.7.40 one lamb of this flock had been sent to the Institute for *post-mortem* examination. A worm count done on it showed 2,100 *Ostertagia* in the abomasum and 50,000 or more *Nematodirus* in the small intestine. Egg counts on the contents of the colon and rectum showed 13,800 eggs of *Nematodirus* per gramme and 3,500 eggs per gramme of other nematodes, presumably *Ostertagia*.

On 26.6.40 the 100 lambs were divided into Groups

Table III.

	Total Weight Before Dose on 27.5.40.	Composite Egg Count Before Dose on 27.5.40.	Total Weight on 20.6.40 (23 days later).	Composite Egg Count on 20.6.40 (23 days later).	Total Gain.
	Group A.	*Given Copper Sulphate.* (10 to 15 *c.c. of 5 per cent. solution according to body weight*)			
Ewes	2,092 lb.	350 e.p.g.	2,186 lb.	0 e.p.g.	94 lb. Average 1·9
Lambs	875 „	50 „	1,033 „	150 „	158 lb. Average 3·1
	Group B.	*Given Phenothiazine Tablets* (*in the proportion of about* 0·1 *gramme per lb. body weight*).			
Ewes	2,033 lb.	850 e.p.g.	2,094 lb.	0 e.p.g.	81 lb. Average 1·6
Lambs	686 „	450 „	821 „	500 „	135 lb. Average 2·7

1 and 2 of 50 lambs each. Each lamb of Group 1 was given 5 grammes of phenothiazine in tablet form (cf. experiment A); each lamb of Group 2 was given 5 to 8 c.c. (according to the size of the lamb) of a solution containing 10 per cent. of copper sulphate and 10 per cent. of a solution containing 40 per cent. of nicotine sulphate. McEwen has informed the writer that he gave for his experiments reported elsewhere in this symposium, 20 c.c. of a solution containing 5 per cent. of copper sulphate and 5 per cent. of a solution containing 40 per cent. nicotine alkaloid. His dose of copper sulphate and nicotine was thus rather more than that given to the lambs used in this experiment. McEwen, however, gave much larger doses of phenothiazine in his experiments, giving 30 grammes to each lamb in his experiment 1 and 10 grammes to each in his experiments 2 and 3.

Faecal samples were taken with the finger from the rectum of each lamb before it was dosed.

The total weight of each group of lambs was ascertained by weighing the lambs on a weighbridge. It was discovered that the weighbridge recorded a difference of 4 to 6 lb. in the weight of each animal according to whether it stood at one or other end of the platform of the machine, while an intermediate weight was recorded when it stood in the middle of the platform. This possible error was reduced to a possible error of 2 lb. or so per lamb by inducing each lamb to stand at the same end of the platform while its weight was being recorded. This experience showed that it is possible to introduce a considerable error into any experiment involving the use of a weighbridge, unless the position of the animal on the platform of the machine is always the same. Another possible source of error in the weights is the normal variation in the weight of each animal before or after a feed or access to water; they should always be weighed at the same time in the day. Further, when faecal samples are being taken from each lamb, it is inevitable that different amounts of faeces will be taken from each, either because the finger cannot take equal amounts from each, or because the second 50 lambs in a group of 100 will have been waiting longer and will often have emptied the rectum before the sample is taken, or because the faeces of some are looser than those of others, so that the finger removes less and there are relatively fewer eggs in the amount of solid removed. When, therefore, all the samples are mixed to form a composite sample on which an egg count is made, it may occur that the egg count is really done mostly on the faeces of the first 50 of the group and mostly on the best-formed faeces of these. It may therefore not represent the average egg content of the faeces of individual lambs.

On the 10th, 20th and 30th days after the doses were given, the lambs were again weighed and faecal samples were taken. Throughout the experiment the lambs were grazing on grass with the rest of the flock and had no extra feed. The following table gives the relevant facts about them.

Table IV.

	Group 1 Given 5 Grammes Phenothiazine in Tablet Form.			Group 2 Given 5 to 8 c.c. of a Solution Containing 10 per cent. of $CuSO_4$ and 10 per cent. of a Solution Containing 40 per cent. Nicotine Sulphate.		
	Total Weight.	Increase.	Eggs per Gramme Average of 2 Counts.	Total Weight.	Increase.	Eggs per Gramme Average per 2 Counts.
26.6.40	2,898 (before the dose)		650	3,162		400
5.7.40	3,367	469 Average 9·38	200	3,837	675 Average 13·5	550
15.5.40	3,200	Loss *167* Average 3·3	200	3,464	Loss *373* Average 7·46	400
26.5.40	4,208	Increase 1,008 Average 20·16	350	3,980	Increase 516 Average 10·3	400
		Total gain in 30 days 1,310 Average 26·2			Total gain in 30 days 818. Average 16·3	

No satisfactory explanation was found of the considerable loss of weight during the second ten days in both groups but especially in Group 2. It may have been partly an apparent loss due to the fact that the lambs were weighed on the first two occasions in the morning and on the second two occasions in the afternoon and that in the afternoon they may have been emptier of grass and water and therefore weighed lighter than they would have done in the morning. But this could hardly have accounted for the whole of the loss of weight recorded, nor for the fact that the loss was twice as much in the group given copper and nicotine. The main fact emerging from this experiment is, nevertheless, that the total gain of weight in 30 days attained by the group given phenothiazine was substantially greater (approaching twice as much) than that of the group given copper sulphate and nicotine. This happened in spite of the fact that only a small dose of phenothiazine was given, namely 5 grammes, whereas 10 to 30 grammes is a normal therapeutic dose. This experiment showed, therefore, that, although at the end of the first ten days the group given copper and nicotine (like the groups given copper sulphate only in experiments A and B) had gained more weight than the group given phenothiazine, by the end of 30 days the group given phenothiazine had done considerably better than the group given copper and nicotine, and a good deal better than the corresponding group in experiment A. This conclusion is supported by a comparison of the composite egg counts. The small dose of phenothiazine reduced this and kept it down at about the same level for 30 days, while copper and nicotine (a normal therapeutic dose) did not appreciably affect it. It may be noted here that Singer and Baker (1940. *Cornell Vet.* **30.** 375-382) found that phenothiazine was more effective than copper sulphate and nicotine or tetrachlorethylene against nematode infestations of sheep.

Further experiments are desirable to ascertain the accuracy of the impression given by this experiment (and to a lesser degree by experiment A also) that the effect of phenothiazine lasts much longer than that of copper and nicotine. If this should prove to be true, the other experiments on sheep and horses, described in this paper, will have an additional interest because they show that egg counts reduced by phenothiazine do not necessarily rise again for many weeks, although the animals are out at grass and are presumably being continuously re-infested.

GOATS

So far only one goat has been available. This was a goat weighing 62½ lb., belonging to a member of the staff of the Imperial Chemical Industries, Manchester. Samples of its faeces were sent by Dr. J. R. M. Innes, who subsequently dosed it with 10 grammes of phenothiazine without toxic effect. Before the dose was given the faeces showed an egg count of 3,650 eggs per gramme (average of two counts).

A sample of faeces collected 24 hours after the dose showed an egg count of 100 (average of two counts). Fourteen days and eighteen days after the dose the egg count was still 100 e.p.g. and 18 days after the dose it was 50 e.p.g. (average of 2 counts). Further samples of faeces will be examined to find out whether the egg count, like that of the lambs and ewes described above, will remain at this low figure for a considerable time.

Attempts to Kill the Ciliates in the Rumen of Sheep with Phenothiazine

On 22.4.40 counts were begun of the ciliates in the rumen of a sheep with a fistula into the rumen. The fistula had been made by Mr. Phillipson, of this Institute, some weeks previously and the sheep was in good bodily condition, weighing 258 lb.

The number of ciliates present was estimated only roughly because it was difficult to count organisms so active as these. The method was to withdraw 2 c.c. of rumen contents, mix it with 98 c.c. water and remove 0·1 c.c. with a pipette. This was diluted with an equal quantity of Lugol's iodine, which killed the ciliates. The ciliates were then counted with the aid of an eye-piece in which hairs crossed at right angles were fixed to divide the field into four parts. The number counted was multiplied by 500 to give the number of ciliates per c.c. After the dose of phenothiazine, the ciliates already dead were first counted in the drop. The iodine was then added to kill the rest, and the number of ciliates was counted again, so that the number alive and presumably not affected by phenothiazine could be estimated. Egg counts were also done, but not more than an average of 50 e.p.g. were found so that the anthelmintic effect of the phenothiazine was ignored.

The daily ciliate counts were :—

22.4.40	576,266	27.4.40	570,000
23.4.40	484,132	28.4.40	Not done
24.4.40	1,463,066	29.4.40	1,013,000
25.4.40	543,000	30.4.40	574,500
26.4.40	448,000		

On 30.4.40 four gelatine capsules, containing six tablets each containing 1 gramme of phenothiazine—a total dose of 24 grammes of phenothiazine—were placed in the rumen through the fistula opening. The sheep thus received a dose of about 0·09 gramme per lb. body weight. Six hours later it was passing red urine. The gelatine of a capsule put into rumen contents in a flask on the previous day and incubated at 38° C. was dissolved in half an hour, and the phenothiazine was set free. It was therefore reasonable to assume that five and a half hours after the phenothiazine became free in the rumen the animal was passing thionol in the urine.

Ciliates were counted in samples of rumen contents taken one, four and twelve hours respectively after the capsules were administered, but no appreciable decrease in the living ciliates was noted. No toxic effects whatsoever were observed in this sheep. The conclusion was therefore that a dose of 0·09 gramme of phenothiazine per lb. body weight directly introduced into the rumen through a fistula did not have any appreciable effect on the ciliates of the rumen.

CALVES

Only one series of calves has been treated. All the calves were about six months old, but their egg counts were not high. They were all dosed at the farm, no change being made in the conditions under which they were kept there. They were all given the first phenothiazine dispersion issued by Imperial Chemical Industries. The table (overleaf) shows the results, and it will be seen that the egg counts of all those which were dosed, except No. 6, were reduced by the dose to 0, but the egg counts of the controls were also very low, so that this result is inconclusive. The results obtained with the marked and unmarked lamb (recorded above) show that it is unlikely that the egg count reduced to 0 would have continued at 0 for very long and that it would probably have been very difficult

TABLE V.

Date.	Kept in a Barn.		Kept Outside in a Compound on Straw.					
	No. 1.	No. 4 Contr.	No. 5.	No. 6.	No. 7	No. 8 Contr.	No. 9 Contr.	No. 10 Contr.
20.10.39	500	No faeces	300	200	100	400	200	100
21.10.39								
22.10.39								
23.10.39	600 Given 100 grammes Phenothiazine	100	0 Given 125 grammes Phenothiazine	150 Given 100 grammes Phenothiazine	100 Given 80 grammes Phenothiazine	200	200	500
24.10.39								
25.10.39								
26.10.39	100	200	100	No faeces	100	200	0	500
27.10.39								
28.10.39								
29.10.39								
30.10.39								
31.10.39	0	50	50	250	0	50	200	150
1.11.39								
2.11.39	0	100	0	100	0	100	0	400
6.11.39	0	0	0	50	0	100	50	400

to keep the egg count at 0. It is likely that 50 to 200 e.p.g. would have remained even after repeated doses. The chief value of this experiment was that it showed that no toxic effects were observed in calves six months old when doses of 80 to 125 grammes of phenothiazine were given.

HORSES

PONIES DRENCHED WITH PHENOTHIAZINE.—Three Shetland ponies and one New Forest pony were offered for experiment by Dr. Hammond of the University of Cambridge School of Agriculture. All these animals were grazing and were kept in the field during the experiment. They ranged in age from three to five years, but the weight of only one was ascertainable at 664 lb. Two were kept as controls and two were given 80 grammes and 60 grammes respectively of the first phenothiazine dispersion issued by Imperial Chemical Industries. This corresponded to a dose of about 0·1 gramme per lb. body weight. No toxic effects were observed, but the day after the dose red urine was passed and the mucosae of the eyes, nose and mouth took on a bronze coloration which gradually waned until it had disappeared four to five days after the dose. It was no doubt due to thionol in the blood.

The egg counts were reduced immediately, dropping from the region of 1,000 to 1,500 until, three days after the dose, they were negative. They remained negative until the ninth day after the dose, when the egg counts were discontinued. After the dose many dead ciliates were found in the faeces. This suggests that phenothiazine kills ciliates which live, as those of the horse do, in the caecum and colon, although the introduction of phenothiazine directly into the rumen contents of a sheep had had no effect on the ciliates there (as recorded above). This is a detail which supports the view expressed by other workers that phenothiazine has more effect on parasites which live in the caecum and colon, a view which suggests that phenothiazine cannot act immediately, but requires time to undergo some change before its toxic action on nematodes is exerted.

HORSES DOSED WITH PHENOTHIAZINE POWDER IN BRAN AND TREACLE.—(1) A longer series of observations was made on a New Forest pony weighing 714 lb., belonging to this Institute. This pony was out at grass throughout the observations and was given 60 grammes of phenothiazine in bran and treacle. The phenothiazine powder now available was not being made when this experiment was done, but 60 tablets, each containing 1 gramme of phenothiazine, were broken up and mixed with the bran and treacle. The egg count showed only strongyle eggs, and although the egg count was not very high, the mean of two daily counts ranging from 350 to 1,150, it had become 0 on the third day after the dose. Egg counts were continued every two or three days and, although the pony was out at grass, they remained negative until the 41st day after the dose, when 150 e.p.g. were present. On the 44th day after the dose 250 e.p.g. were found, and on the 48th day 100 e.p.g. The pony was therefore then acquiring a slight reinfestation. No toxic effects whatever were observed in this animal. It grazed on the same pastures until 24.6.40, when the average of two egg counts was 400. A further infestation was thus being established then.

(2) *Thoroughbred* 3 was given 40 grammes of phenothiazine powder, prepared in a similar way, a dose of about 0·2 gramme per lb. body weight, in bran and treacle with a similar result. The mean of two daily egg counts on this horse ranged from 150 to 800 for a period of 23 days before the dose. This horse was kept indoors in a box throughout the observation. The day after the dose, its mucosae were bronzed, but were practically normal again in four days and quite normal seven days after the dose. The blood of this horse was examined spectroscopically on the first and second days after the dose, but nothing abnormal was found in it. No toxic effects were observed. The egg count became negative on the second day after the dose and remained so until the eleventh day after the dose when the experiment was discontinued.

THOROUGHBREDS GIVEN PHENOTHIAZINE POWDER IN WATER BY STOMACH TUBE TO TEST ITS TOXICITY

Thoroughbred 2.—This mare, two years old, 952 lb. in weight, was given 500 grammes of phenothiazine powder obtained by crushing up in water tablets each of which contained 1 gramme of phenothiazine. The

suspension was given through a stomach tube. The object of this very large dose, amounting to rather more than 0·5 gramme per lb. body weight, was to test the toxicity of the drug. There were so few eggs in the faeces that this animal was not suitable for observation of the anthelmintic efficiency of the drug. On the day after the dose the animal was off its food and was passing red urine. The mucosae were bronzed and there were petechial haemorrhages in the vulva around the vestibule, possibly due to irritation by the urine. On the second day after the dose, the animal was normal again and remained so until the fourth day after the dose, when the mucosae were practically normal in colour. The animal had evidently suffered no serious ill-effects from this large dose.

Forty-nine days after this large dose, a second dose of 500 grammes was given, also by stomach tube. This time the phenothiazine powder that had just been introduced by Imperial Chemical Industries was used in water. This large dose was given in the morning. At 3 p.m. the same day the animal was uneasy, showed evidence of intestinal discomfort, and would not feed. The mucosae of its eyes and mouth were already bronzed and the urine thick and chocolate-coloured. Possibly the intestinal discomfort was due to the mechanical effects of the bulk of the drug in the stomach, because by the next morning the animal was feeding well and seemed fairly fit. The mucosae were still bronzed and the urine red. Blood submitted to Professor Keilin for spectroscopic examination showed an increase of about 10 to 12 per cent. of methaemoglobin which suggested that the phenothiazine had produced some oxidation of the haemoglobin, but the amount of methaemoglobin was not accurately estimated. No sulphhaemoglobin was present and the blood did not show any other abnormality. On the following day the methaemoglobin was only slightly reduced, but by 16.1.40, eight days after the dose, it had practically all disappeared. In blood, taken two days after the dose, the haemoglobin index was 83 per cent. and the red cell count 6,037,500, the colour index being 0·7 ; two days later the haemoglobin index was 78 per cent. and the red cell count 6,818,000, the colour index being 0·58. On the eighth day after the dose, the haemoglobin index was 81 per cent., the red cell count 7,000,000 and the colour index 0·578. These figures are within the normal variations shown by the blood of healthy horses.

The day after the dose, a number of dead strongyles were recovered from the faeces, some containing eggs, others being flattened and pigmented brown. These were identified as mature and immature *Trichonema* spp.

On the second day after the dose, the animal was still listless, but brighter than the day before. Its temperature was 92·2°, and the limbs were cold. It ate hay, but little else ; the mucosae were still bronzed and the urine red ; in the afternoon the temperature had risen to 100·2° and a bran mash was refused. On the third day after the dose the animal was still listless, with a morning temperature of 100° and an afternoon one of 99·2° and red urine and bronzed mucosae. Rather more food was taken and the condition was on the whole better. On the fourth day after the dose the temperature was as for the third day, the mucosae almost normal, the urine still red and the animal was eating hay only.

On the fifth day after the dose the morning temperature was 100·6°, the mucosae about the same, the urine still red, but the animal was much brighter and was feeding better.

On the seventh day after the dose the mucosae were still slightly bronzed, especially above the teeth, the urine was still red and the bowels loose, but the animal was feeding well and in quite good condition.

By the eighth day after the dose, when the spectroscopic blood examination showed that very little methaemoglobin was left, the urine was still red. It did not become normal till the tenth day when the mucosae were also normal and the animal had fully recovered.

This history is interesting because it shows that a second large dose of 0·5 gramme per lb. body weight given to a young horse was definitely toxic, whereas the previous dose had had little toxic effect. The interpretation of this result is difficult, but it is worth noting, because it may indicate that successive doses must be given with care. It is possible that one dose may sensitise an animal for some time. On the other hand, the dose given to this horse was excessively large and its very bulk may have caused most of the trouble. There is no record of ill-effects in horses from repetition of the small doses and there is evidence in the literature that, in other animals, repeated small doses do not have toxic effects and may be more effective than larger single doses. The experiments with pigs recorded below suggest that the age of animals dosed is an important factor. A note on the effects of relatively large doses recently given to young foals by F. Day, F.R.C.V.S., will be sent to the *Veterinary Record* as soon as possible.

Thoroughbred 1.—Another mare, 9 years old, and weighing 1,232 lb., was given 1,000 grammes of phenothiazine powder obtained by crushing up in water tablets each of which contained 1 gramme of phenothiazine. The suspension was given by stomach tube, the object of the very large dose being to test the toxicity of the drug. There were so few eggs in the faeces that this animal was not suitable for observation of the anthelmintic efficiency of the drug. The day after the dose was given, this animal would not feed and was passing red urine and its mucosae were bronzed. It was restless and in some pain all day. On the second day after the dose it seemed better and one dead *Ascaris* was found in the faeces. Early on the third day after the dose, the animal was very restless and still would not feed. At 2.30 p.m. she was down and struggling for breath with staring eyes and was obviously in great distress. She was got up, but walked very stiffly. The temperature was 103°, the pulse rapid and weak, she was sweating a little and the ears were cold. At 4.30 p.m. she was destroyed.

The following extract from the note published by Innes and Whittick on this horse shows that, in their opinion, most of the symptoms shown by this animal were due to a thrombo-angiitis, rather than to the phenothiazine. It is difficult, however, to resist the conclusion that the condition found in the stomach and kidneys was caused by the drug. The case must remain inconclusive, but it is clear that a dose as high as 1 gramme per lb. body weight should not be given to horses. It is not likely ever to be given, because the experiments done with other horses show that 0·1 gramme per lb. body weight is an efficient anthelmintic dose.

Extracts from—Innes, J. R. M., and Whittick, J. W. (1940.) *J. Path. and Bact.* **50.** 377-381. "Thrombo-angiitis obliterans in a Horse."

Summary of *post-mortem* findings " :—

" Pulmonary embolism ; thrombosis of termination of the abdominal aorta ; occlusion of the large arteries of both hind limbs by thrombus and mural thickening ; thrombosis and thickening of some veins in the hind limbs ; numerous acute haemorrhagic erosions in fundus of stomach ; subendocardial haemorrhage in left ventricle and right atrium ; congestion of lungs ; areas of mucosal necrosis and ulceration in renal pelves and ureters, probably attributable to the toxic action of the drug ; no oedema of the limbs."

On subsequent page the authors say :—

" There was no evidence of verminous infestation in any of the vessels.

" The vascular lesions are definitely those of organised thrombosis and, in the absence of cardiac disease and of arteritis due to *Strongylus* larvae, the assumption of primary arterial disease of the vessels of the hind limbs seems to be justified.

" Thrombosis of the veins in this horse was probably secondary to slowing of the blood flow consequent upon the arterial obstruction.

" The arterial changes, because of their chronicity, cannot be attributed to the action of phenothiazine, although the drug in the dose given may have been toxic and may have precipitated the final illness."

PIGS

In the colons of two pigs received at the Institute, from a farm, nodules resembling those produced by *Oesophagostomum* were found, although no worms or larvae could be found in them.

Phenothiazine powder, derived from the breaking up of 1 gramme tablets, was given to these pigs. They were all about three months old and their average weight was 35 lb.

The pigs were divided into Groups A, B and C of ten pigs each and a group of undosed controls. The pigs in Group A were dosed and weighed individually, each pig being given 0·5 gramme per lb. body weight of phenothiazine. For the pigs in Groups B and C enough phenothiazine was weighed out to give the pigs in Group B 0·2 gramme per lb. body weight and those in Group C 0·1 gramme per lb. body weight. The total dose for each group was then mixed in the trough with the food and the pigs were allowed to eat it, the intention being to repeat the dose of 0·1 and 0·2grammes per lb. body weight if no ill effects were seen. The pigs took the doses well, but there was no certainty that each pig got an equal amount of phenothiazine.

Group A, given 0·5 Gramme per lb. Body Weight, Dosed Individually.—The day after the dose one pig of this group was brought to the Institute unconscious and waving its legs in the air. It subsequently recovered by the fourth day. Other pigs were similarly affected, but less seriously, showing only drunken gait, inability to turn corners and weakness of the hind legs. All of these subsequently recovered. The dosing was not repeated.

Group B, given 0·2 Gramme per lb. Body Weight as a Mass Dose in the Feed.—The day after the dose one pig only showed some slight weakness in the hind legs. A second dose of 0·2 gramme per lb. body weight was given on the second day. On the third day six pigs showed complete loss of co-ordination, but recovered by the fourth day. The dose was not repeated after this second dose.

Group C, given 0·1 Gramme per lb. Body Weight as a Mass Dose in Feed.—After the first dose no pigs showed any symptoms and on the second day a second dose of 0·1 gramme per lb. body weight was given. The day after this second dose three or four pigs showed slight rolling gait and inco-ordination, but all recovered. The dosing was not repeated, so that these pigs had had two doses on successive days of 0·1 gramme per lb. body weight, 0·2 gramme per lb. in all.

Two months later it was adjudged that all the pigs which had had phenothiazine were in better condition than those which had not. The weight increase, however, was roughly the same in the dosed groups and in the undosed controls.

The impression gained from this inconclusive experiment was that the method of dosing was responsible for the ill-effects observed. Only a few of the pigs were adversely affected, which suggested that these obtained more food and therefore more than their allotted dose of phenothiazine. This the writer had expected, but it was thought worth while to see if this method of dosing was safe in practice. The following additional experiment suggests that an overdose of the drug obtained in this way was probably the correct explanation of the ill-effects.

Twenty-seven pigs about three months old, undergoing a metabolism experiment at this Institute, with an average weight of 42 lb., were each given individually 0·1 gramme per lb. body weight of the 5 gramme tablets of phenothiazine now being made by Imperial Chemical Industries. The pigs were starved for 24 hours before the dose was given. They were being fed individually so that they could be dosed individually by mixing the dose with the feed.

None of the pigs showed any visible ill-effects. None showed any inco-ordination. The exact weighings of each of the ingredients of the rations that were being given to them indicated that the food intake of some of the pigs was reduced after the drug was given, although no visible effects on the animals could be noted. After five days all the pigs had resumed their normal intake of food. There is as yet no clear proof that this reduction in food intake was due to the phenothiazine.

Two other pigs of the same lot as the above 27 and the same age were also dosed individually as follows :—

One weighing 61 lb. was given 0·1 gramme per lb. body weight of phenothiazine tablets and showed no visible ill-effects. Four days later, when its urine was no longer red, it was given 0·5 gramme per lb. body weight without visible ill-effects.

The other, weighing 37 lb. was given 0·14 gramme per lb. body weight without visible ill-effects and four days later it was given 0·2 gramme per lb. body weight without visible ill-effect.

These observations, inconclusive as they are, do indicate that pigs three months old dosed individually with 0·1 gramme phenothiazine per lb. body weight do not suffer any visible ill-effect. When the dose for a number of pigs is mixed in the feed and the pigs are allowed to take it as they will, there is danger that some will get too much and will suffer accordingly.

Larger doses will in the near future be given to pigs individually and the results will be compared with those of Swanson, Harwood and Connelly (1940) *J. Amer. vet. med. Ass.* **96**, 333-338), who gave up to 1 gramme per lb. body weight to older pigs without toxic effects. Meanwhile, it is probably wise to give phenothiazine to *young pigs* with great care. The *Ascaris* burden of the pigs described above was

not removed, nor much influenced, by this dose of phenothiazine. The reason for this is not clear.

Summary

(1) Two lambs weighing 74 lb. and 89 lb. were given 0·3 gramme and 0·27 gramme per lb. body weight respectively of phenothiazine in the form of tablets. Three days after the dose the egg count had fallen, in the one case, from 7,400 e.p.g. to 200 e.p.g. and, in the other, from 3,850 to 550 e.p.g., these egg counts being the mean of two counts done by different observers on different portions of the same sample of faeces. The egg counts of both lambs, which were kept in a box together, remained round about this figure for rather longer than five months. Attempts to reduce the egg count to 0 and to maintain it at 0 by giving further doses of phenothiazine were not successful.

It is never desirable to remove all the nematodes from any animal because this procedure will lower or remove the host's resistance to the infestation.

(2) Comparisons of the effect of phenothiazine, copper sulphate and copper sulphate and nicotine on nematode infestations of ewes and lambs in the field indicated that small doses (about 0·1 gramme per lb. body weight) of phenothiazine lowered the egg counts more effectively than did either of the other two anthelmintics and tended to maintain them more effectively at a lower level. In three experiments 157 ewes and lambs were weighed every ten days for a period of 30 days after doses of about 0·1 gramme per lb. body weight of phenothiazine. The results indicated that, even when these small doses are given, the weight increase of animals given phenothiazine is significantly greater at the end of 30 days than that of animals given normal therapeutic doses of copper sulphate or copper sulphate and nicotine, although, during the first 20 days or so, the animals given these two latter anthelmintics appear to put on slightly more weight. The egg counts of the animals given phenothiazine were reduced more effectively than those given the other two anthelmintics and remained low. It is thus possible that phenothiazine has a more lasting anthelmintic effect than copper sulphate and copper sulphate and nicotine, perhaps because it prevents the development of a second generation of worms picked up from the pasture. Further experiments on this question are in progress.

It is unlikely that a copper deficiency in the animals used contributed in any way to these results, because there was no evidence of this and swayback had never been reported from the district in which the animals used were bred.

(3) No toxic effects were shown by any of the sheep treated with these doses of phenothiazine. It was not expected that the small doses used would have any toxic effects.

(4) A similar marked fall in the egg count of a single goat from 3,650 e.p.g. to 150 e.p.g. was noted 24 hours after it had been given, without toxic effect, a dose of 0·15 gramme per lb. body weight of phenothiazine.

(5) Attempts to kill the ciliates in the rumen of a sheep by introducing phenothiazine powder into the rumen through a fistula did not kill any appreciable number of the ciliates. Thionol appeared in the urine of the sheep 5½ hours after phenothiazine was set free in the rumen.

(6) Doses of 80 to 125 grammes of phenothiazine did not produce any visible toxic effect in calves six months old.

(7) The passage of red urine and bronzing of the mucosae, which usually persists for four days or so after the administration of phenothiazine, was noted in all the sheep, horses and calves treated. When the doses were larger, loss of appetite and listlessness were noted. These are signs that the dose should not be increased, nor repeated until a considerable interval has elapsed.

(8) Phenothiazine powder at the rate of about 0·1 gramme per lb. body weight administered to horses, either mixed in a feed of bran and treacle or given suspended in water with a stomach pump, reduced the strongyle egg count to 0, or near that figure, and the egg count did not rise again appreciably for many weeks, although the horses were at grass.

(9) One horse, given 500 grammes of phenothiazine in water with a stomach pump (a dose of about 0·5 gramme per lb. body weight) suffered little more than transient loss of appetite and listlessness. After the same dose 49 days later the same horse became restless and uncomfortable and refused to feed for a few days, but subsequently recovered. Another horse, given 1,000 grammes with a stomach pump showed marked toxic effects, but the existence in this animal of thrombo-angiitis rendered it impossible to say whether the symptoms were due to this disease or to the phenothiazine. Examination of the blood of these horses showed no other abnormality than a transient excess of methaemoglobin.

(10) Evidence is given which suggests that phenothiazine should be administered to young pigs with great care, although doses of 0·5 gramme per lb. body weight appear to have no toxic effects on mature pigs.

* * * * *

Comparative Tests on the Treatment of Lambs with Phenothiazine and with Copper Sulphate and Nicotine Sulphate

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Experiment 1

This experiment was carried out in co-operation with Dr. E. L. Taylor and the experimental animals were purchased and maintained at the expense of the Veterinary Laboratory, Ministry of Agriculture, Weybridge.

A flock of 123 lambs, seven to eight months old, was placed in experiment in November, 1939. The animals were divided into three groups, each containing 41 lambs, and they were kept throughout the experiment on a limited range of permanent pasture that had been heavily stocked with sheep.

Group 1 was treated every two weeks with 30 grammes of phenothiazine.

Group 2 was treated every two weeks with 20 c.c. copper sulphate and nicotine sulphate.*

Group 3 was left untreated as a control group.

The lambs were weighed every two weeks. Treatment began on December 11th, 1939, and the lambs were dosed ten times, the last treatment being given on April 29th, 1940. The final weighing was made on May 20th, 1940. The lambs were sold by public auction on June 7th, 1940

* The mixture used contained approximately 5% copper sulphate and 5% " nicotine sulphate 40 solution,"

Table I.
Showing Death Rate and the Sums for which Animals were Sold

Group.	No. in Experiment.	No. Died.	No. Survived.	No. Sold.	Amount.
					£ s. d.
1	41	10	31	30	52 17 6
2	41	8	33	31	51 5 0
3	41	21	20	19	28 10 0

Table II
Showing the Mean Weights

Date Weighed.	Group 1.	Group 2.	Group 3.
11.12.39	71	72	74
22.12.39	68	69	71
8.1.40	68	70	69
5.2.40	62	63	61
19.2.40	64	64	61
4.3.40	61	59	58
18.3.40	63	59	58
1.4.40	65	61	59
15.4.40	69	65	61
29.4.40	74	71	68
20.5.40	83	82	75

In Table 2 are shown the mean weights of the three groups at various intervals after the commencement of the experiment. It may be stated that from March 18th onwards, the mean weight of the lambs in Group 1 was significantly higher than that of the lambs in Group 3. The animals in Group 2 occupy an intermediate position between Groups 1 and 3, and this suggests that phenothiazine is the better of the two anthelmintics.

Experiment 2.

In this experiment the dose of phenothiazine was reduced to the smaller and more convenient one of 10 grammes; the 20 c.c. dose of copper sulphate and nicotine sulphate was retained. Fifty-four of the poorest lambs, in a flock showing evidence of parasitic gastritis and enteritis, were selected and divided into two approximately equal groups. The lambs in Group 1 were given phenothiazine and those in Group 2 were given the copper sulphate and nicotine sulphate mixture. No controls were kept. The lambs were first weighed and treated on March 18th, 1940. Altogether the lambs were dosed four times at fortnightly intervals and on each occasion they were weighed. Their weights were taken for the fifth and last time on May 20th, 1940.

Table III
Showing the Mean Weights of the Lambs.

Date Weighed.	Group 1.	Group 2.
18.3.40	71	67
1.4.40	72	68
15.4.40	77	72
29.4.40	83	78
20.5.40	96	87

It may be stated that at the last weighing the difference of 9 lb. between the mean weights of the two groups was found to be statistically significant. The experiment therefore suggests that phenothiazine is the better anthelmintic.

Experiment 3.

Observations were made on three flocks of 11 to 12 month-old lambs belonging to the same owner. Each flock of lambs was divided into two equal groups and one group was treated with phenothiazine while the other received copper sulphate and nicotine sulphate. The dose of the former was 10 grammes and the dose of the latter 20 c.c. The animals were not weighed and the effects of the two different treatments were compared from the appearance of the animals approximately three weeks after treatment stopped.

Flock 1 consisted of 86 lambs; treatment began in March and the animals were dosed three times at intervals of three to four weeks.

Flock 2 contained 45 lambs; treatment began in April and the lambs were dosed twice.

Flock 3 contained 30 lambs and they were dosed in the latter part of April.

The lambs were inspected in May, between two to three weeks after the last treatment had been given. Each flock was divided into its two groups that were held for examination in adjacent sheep pens. Without knowing the treatment given to each individual group I selected the better group in each flock and in all three cases this proved to be the group that had been treated with phenothiazine. The superior condition and bloom of the lambs that received phenothiazine was most marked in the flock that had been treated for the longest period and had been dosed three times. In the flock that had been treated on one occasion only, the difference was least obvious. In each case my selection of the better group was confirmed later on in the same day by a shepherd who was not aware that the animals had been treated. These observations again suggest that phenothiazine is the better anthelmintic.

Summary

Comparative tests made on five flocks of lambs indicate that phenothiazine is a more effective anthelmintic than copper sulphate and nicotine sulphate.

* * * * *

Phenothiazine in Parasitic Gastritis

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The results of small scale experiments in Australia showed that phenothiazine was of value in treating parasitic gastritis in sheep. The following is the account of an experiment carried out in North Wales. In no case, however, could the sheep be regarded as typical cases of acute parasitic gastritis.

Farm A.

Eleven wether (Welsh) lambs—" culls "—showed symptoms of scouring, extreme emaciation, poor fleece and increased lacrimation. They had been grazing on a permanent pasture and had ceased thriving from the end of August. They had been dosed at intervals with proprietary worm pills.

A *post-mortem* examination of an emaciated lamb showed the following worms to be present:—

4th Stomach—1,600 ...	*Haemonchus contortus*	100
	Ostertagia	1,100
	Trichostrongylus ...	400
Small Intestine—15,200	*Haemonchus contortus*	7,296
	Trichostrongylus ...	5,472
	Cooperia	2,432

The lambs were divided into two groups; the six poorest were dosed with 20 grammes phenothiazine (tablet form) crushed and suspended in water and drenched on December 1st. Five lambs acted as controls, receiving no treatment. All the lambs were weighed prior to dosing and two composite faeces samples consisting of the faeces of each individual lamb in each group were taken. The results are set out below:—

Group.	Date.	Average Weight.	Average Loss in Weight.	Average Egg Count.
Dosed ...	1.12.39	34·7 lb.	0·4 lb.	2,100
	20.12.39	34·3 „		400
Undosed ...	1.12.39	44·2 „	1·8 „	1,700
	20.12.39	42·4 „		600

Farm B.

This is an upland farm and the flock consisted of 73 ewes, 2 rams, and 15 lambs. There were no obvious clinical symptoms, except those of poor thriving, the condition being due, in part at least, to the poor pasture. After weighing a fair proportion of the dosed and undosed ewes and lambs and obtaining two composite faeces samples, 53 ewes, 2 rams and 10 lambs were drenched with 20 grammes phenothiazine, 20 ewes and 5 lambs being left as controls. The results are shown in the table at the top of the next column.

	Group.	Date.	Average Weight.	Average Loss in Weight.	Average Egg Count.
Ewes	Dosed ...	1.12.39	59·0 lb.	3·9 lb.	300
		29.12.39	55·1 „		Nil
	Undosed	7.12.39	60·0 „	6·0 „	Nil
		29.12.39	54·0 „		Nil
Lambs	Dosed ...	7.12.39	43·6 „	3·8 „	300
		29.12.39	39·8 „		Nil
	Undosed	7.12.39	42·4 „	5·0 „	100
		29.12.39	37·4 „		400

Two further experiments were carried out on a small group of lambs at the laboratory. Five wether lambs that previously grazed upon a permanent pasture on the College Farm, Aber, were treated. Particulars of dosage, egg counts and weights are set out in the accompanying table and appear to indicate a marked beneficial result from the use of phenothiazine.

Five wether lambs from a farm where losses had been comparatively heavy were sent to the laboratory. A *post-mortem* examination on one lamb that died had revealed the presence of 1,200 nematodes in the fourth stomach and 1,100 in the small intestine. Two weeks later 20 grammes phenothiazine was administered to the four lambs. A *post-mortem* examination on one of them which died shortly afterwards showed the complete absence of parasitic worms,

Table: *Showing the Effect of Phenothiazine in Reducing the Worm Infestation in Five Experimental Lambs.*

Date.	L.1.			L.2.			L.3.			L.12.			L.17.		
	Treatment.	Weight in lb.	E.P.G.	Treatment.	Weight in lb.	E.P.G.	Treatment.	Weight in lb.	E.P.G.	Treatment.	Weight in lb.	E.P.G.	Treatment.	Weight in lb.	E.P.G.
7.11.39		50	1,100	10 grammes Phenothiazine	35	2,000	10 grammes Phenothiazine	40	600	15 c.c. Nicotine mixture	45	700	15 c.c. Nicotine mixture	45	5,100
5.11.39		41			43	700	Died 13.11.39*				49	1,900		51	1,300
29.11.39	18 grammes of Phenothiazine	40	1,100	1.12.39 20 grammes Phenothiazine	43	600					50	600		51	700
13.12.39		45	300		43	1,000					51	400		49	1,000
28.12.39		46	100		46	nil					44	300	21.12.39; 20 grammes Phenothiazine	48	nil
12.1.39	11.1.39; 60 grammes Phenothiazine	52	nil		50	nil				11.1.39; 50 grammes Phenothiazine	48	nil		51	nil
26.1.39		54	nil		53	nil					49	nil		57	nil
6.2.39		56	nil		50	nil					50	nil		60	nil
Increase in weight over experimental period		6			15						5			15	

* *Post-mortem* examination showed no worms in abomasum and only 300 in small intestine.

eggs disappeared from the faeces of those remaining alive and their general bodily condition became greatly improved.

Conclusion and Summary

(1) Phenothiazine is a very efficient anthelmintic in sheep, providing the dose is sufficiently high—20 grammes or more.

(2) Phenothiazine is well tolerated, 60 grammes having been given to a 50 lb. lamb without ill effects.

(3) Phenothiazine is best administered in liquid form, with the aid of a dosing syringe.

(4) Before phenothiazine is administered owners should be warned of the red colour that it produces in the urine.

* * * * *

Report on Phenothiazine as an Anthelmintic in Horses*

T. GRAHAME, D. O. MORGAN and J. E. N. SLOANE.

Object of Investigation.

The object of the investigation was to determine:

(1) The efficiency of the drug as an anthelmintic.
(2) A simple method of administration of the drug.
(3) The reaction of the animal to the drug.
(4) The minimum effective dose.

Selection of Animals.

The first batch of horses examined had been in the barrack stables some time prior to the outbreak of the war.

The subsequent examinations were made on remounts; these horses were from units in various parts of England and Scotland, and the majority had been newly acquired by the Army.

Each animal was subjected to a routine examination and weighed, and special attention was paid to the teeth, faeces and blood. The drug was not given to any animal that showed any deviation of temperature or pulse.

Apparent poor condition was not always an indication that the animal had a high infestation of helminths, and, conversely, neither was good condition invariably an indication of a low infestation. It was discovered that many of the debilitated poor " doers " had a low or almost negative count, whereas many animals which appeared to be in " good condition " were heavily infested; these animals were treated.

Practically all the horses, whether in good or bad condition, improved and gained in weight following the administration of the drug.

All the animals chosen were infected with strongyles and occasionally with ascarids.

Administration of the Drug.

The data on the use of phenothiazine as an anthelmintic in the horse is somewhat scanty, and the dosage, method of administration, etc., required further investigation. The first doses given in the present series were based on 5 grammes per 50 lbs. body weight, which usually worked out at approximately 100 grammes for the average cavalry horse.

One hundred grammes of phenothiazine is a bulky mass, and its administration offered a problem. The powder is not miscible in water, but may be suspended and given by stomach tube.

The administration of the powder in the food was tried with success. The procedure was to feed a bran mash mixed with treacle, followed at the next meal by a similar feed with which the powder was mixed. Some animals reluctantly ate the mixture, while others, especially the " particular feeder," left it. The following method was found to be the most satisfactory. The animals were made to miss a feed, and then an ordinary bran mash containing the powder was given. In almost every case the feed was eaten, and there was no difficulty when a little boiled oats was added.

It was the usual practice to treat the animals at the week-end, missing the Saturday morning feed and giving a meal containing the powder at the midday feed. In this manner the usual routine of work was not interfered with. The animals were at their usual work on Monday, having suffered no apparent inconvenience. However, to prevent the working of any horse that might be particularly sensitive to the action of the drug, each animal was examined every morning for a week subsequent to the administration of the medicine.

Reactions of the Drug.

Some interesting observations were made which seem to have a bearing upon the distribution and possible " breakdown " of the drug in the body system, although some horses showed little or no departure from the normal:

(1) The conjunctival mucous membranes were stained a yellowish colour and occasionally the mucous membranes of the mouth and anus were similarly coloured. The yellow coloration appeared after 24 hours and sometimes became more intense, but gradually faded out. In some, the coloration disappeared in a few days, but in others it persisted for seven to eight days and even longer. The mucous membranes of the mouth and anus were stained a faint yellow, very much less intense than that of the conjunctiva.

(2) The urine of some horses was viscid and coloured a reddish brown. Attention is drawn to this condition by the staining of the bedding and floor of the stable, and by the red-bespeckled hind limbs, especially noticed when the limbs have white markings.

The coloured excretions may persist for two to four days. In several animals, the urine remained coloured for several days before a clearance was effected.

Those unaware of this action of the drug might be alarmed and consider the reaction unfavourably. Analysis of the urine did not show any unusual ingredients, other than might be expected from the " breakdown " of the drug.

Technique.—To measure the anthelmintic efficacy of the drug, egg counts were carried out before and after dosing.

The modified Stoll dilution method was used throughout: 5 grammes of faeces were weighed out into a jar graduated at 75 c.c. and N/10 NaOH

*An investigation conducted under the co-ordination of The Helminths Committee (Animals Section) of the Agricultural Research Council.

added up to the 75 c.c. mark. The sample was left overnight to soften, and after shaking and sieving to remove coarse debris, 0·15 c.c. was removed by means of a Macdonald pipette. All the eggs in the 0·15 c.c. were counted, and the process was repeated three or four times, and the average count taken. The figure obtained, multiplied by 100, gave the number of eggs per gramme of the original sample. Eggs of *Parascaris equorum* were counted separately from those of strongyle worms. The faeces were taken direct from the rectum of each horse.

Explanation of Tables.—Where a count of 30 eggs appears in the tables, this indicates that only one egg was seen in the three slides examined. A plus sign in the tables indicates that no eggs were found by the above counting technique, but that a concentration method using about 5 grammes of faeces revealed a few eggs.

Owing to the transfer of horses, some irregularity occurred in respect of the intervals of time between the three counts after dosing. In Tables I, II, III, VII, and VIII, the counts were made at approximately two, four and six weeks after dosing, and in Tables IV, VI, IX and X at two, three and four weeks. In Table V, only one count was obtained, and this was taken at four weeks. In every case where a third count was obtained, it was taken at not less than four weeks after the date of dosing.

TABLE I

Results obtained from the administration of 100 *Grammes of Phenothiazine Powder*

Horse No.	Age.	Strongyle Eggs per Gramme. Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
A38	11	1,000	0	0	330
A39	11	1,400	0	0	230
A42	6	850	0	0	+
A46	8	560	+	+	130
A47	8	1,000	0	0	60
A50	9	600	0	0	30
A52	6	1,050	0	0	60
A79	15	1,200	0	0	30
A86	11	750	0	0	360
A89	8	800	+	+	160
A91	6	800	+	+	+
A99	9	1,560	+	+	+
B40	10	600	0	0	0
B44	7	400	0	0	0
B46	9	1,060	+	30	60
B51	6	260	+	30	130
B54	8	1,330	0	+	30
B58	8	830	30	60	260
B59	8	1,400	0	0	+
B68	8	60	0	0	0
B69	6	1,160	0	0	+
B70	8	600	+	+	+
B72	7	600	0	0	60
B73	15	460	0	0	+
B76	14	1,780	0	0	260
B77	12	450	0	+	60
C60	14	1,300	230	200	260
C61	7	1,360	+	+	60
C66	15	1,430	+	+	30
C70	12	1,200	0	0	+
D 2	8	630	0	30	130
D28	10	250	+	+	+
D36	6	1,000	+	+	100
D45	9	970	0	0	+
t.b.d.	2	970	+	+	+

TABLE II

Results obtained from the administration of 95 *Grammes of Phenothiazine Powder*

Horse No.	Age.	Strongyle Eggs per Gramme. Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
C59	15	2,500	0	0	130
C72	9	1,030	0	0	+
C75	15	1,030	0	+	+

TABLE III

Results obtained from the administration of 80 *Grammes of Phenothiazine Powder*

Horse No.	Age.	Strongyle Eggs per Gramme. Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
A44	7	960	0	0	+
B63	8	1,060	+	+	130
B75	6	560	+	+	+
B8	9	630	330	200	200
D49	10	700	0	0	230

TABLE IV

Results obtained from the administration of 4 *fl. oz. Phenovis* = 72 *Grammes of Phenothiazine Powder*

Horse No.	Age.	Strongyle Eggs per Gramme. Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
A 7	10	1,200	0	0	0
A33	13	60	0	0	60
A48	6	1,300	+	+	+
A56	7	600	0	0	0
A59	13	300	0	0	+
A73	10	500	0	0	0
A75	8	800	0	0	0
A76	6	500	0	0	0
A80	15	830	0	0	0
A84	12	500	0	+	+
A92	12	560	0	0	0

Table V

Results obtained from the administration of 60 Grammes of Phenothiazine Powder

Horse No.	Age.	Strongyle Eggs per Gramme.	
		Count Before Dosing.	Count After Dosing.
B31	9	1,000	30
B35	15	300	160
B39	10	130	30
B41	8	700	0
B42	15	1,630	0
B43	9	660	30
B49	8	500	0
B52	6	730	30
B55	11	820	30
B57	14	800	60

Table VI

Results obtained from the administration of 3 fl. oz. Phenovis = 52 Grammes of Phenothiazine Powder

Horse	Age.	Strongyle Eggs per Gramme.			
		Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
A64	6	130	0	0	0
A72	8	560	0	0	0
B 9	8	1,100	60	60	60
B13	13	800	0	0	0
B18	12	1,500	+	+	60
B21	8	300	+	+	+
B23	11	800	0	0	+
B27	15	1,430	0	0	0
B29	9	2,460	0	0	0
B37	12	800	+	30	30
D85	15	1,860	0	+	360

Table VII

Results obtained from the administration of 35 Grammes of Phenothiazine Powder

Horse No.	Age.	Strongyle Eggs per Gramme.			
		Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
D81	10	1,600	+	+	120
D83	8	2,060	320	520	1,120
D84	8	2,000	0	0	200
D86	7	1,520	0	0	60
D87	7	1,060	0	0	120

Table VIII

Results obtained from the administration of 30 Grammes of Phenothiazine Powder

Horse No.	Age.	Strongyle Eggs per Gramme.			
		Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
D90	8	1,400	0	0	120
D91	10	1,200	0	+	260
D92	7	1,000	0	0	Destroyed
D93	11	1,120	0	60	120
C50	9	860	+	60	320

Table IX

Results obtained from the administration of 25 Grammes of Phenothiazine Powder

Horse No.	Age.	Strongyle Eggs per Gramme.			
		Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
C37	14	2,800	120	120	600
C65	7	2,000	400	520	720
C71	7	1,320	60	60	600
C72	10	1,400	320	320	400
C77	15	1,060	60	60	400

Table X

Results obtained from the administration of 20 Grammes of Phenothiazine Powder

Horse No.	Age.	Strongyle Eggs per Gramme.			
		Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
D49	10	1,400	320	460	660
C 1	10	1,320	520	860	800
C15	6	860	400	520	460
C21	6	1,060	120	400	400
C24	7	1,200	60	60	60

TABLE XI

The following Table is compiled from the preceding Tables and gives Egg Counts for Parascaris equorum

Horse No.	Age.	Ascaris Eggs per Gramme. Count Before Dosing.	1st Count After Dosing.	2nd Count After Dosing.	3rd Count After Dosing.
A42	6	330	0	0	0
A52	6	60	0	0	0
A64	6	30	+	+	30
A86	11	60	0	0	30
A91	6	30	0	0	0
B54	8	30	0	0	0
B59	8	60	0	0	0
B68	8	60	0	0	0
B77	12	30	130	60	0
D28	10	100	60	30	30
D36	6	50	100	100	30

DISCUSSION

After doses ranging from 30 to 100 grammes, the first two egg-counts were negligible, except in a very few cases. In the third count, on the other hand, a slight rise was found in the majority of cases. This figure, however, is very small in comparison with the count before dosing and is no more than might be expected in view of the lapse of time between the times of dosing and the third count. The increase may be explained by the maturing of larvae which were in the tissues at the time of dosing, and which had returned to the lumen of the gut in the interval.

Doses of less than 30 grammes, however, did not produce comparable results, although a notable reduction in the egg-count was recorded, for the 25 grammes group of approximately 80 per cent., and for the 20 grammes group of 40 per cent. In these two groups the second and third egg counts show a rapid increase, and it would seem that while the drug did not kill all the worms; nevertheless it affected the egg-laying activities of the females for a period of nearly three weeks.

On the evidence set forth in the above tables, the minimum effective dose is considered to be approximately 30 grammes.

Only 11 horses of the total of 95 treated, harboured *Parascaris equorum,* and infestations were light in all cases. No definite conclusions can therefore be drawn from these observations concerning the value of the drug against this parasite, and although the egg-counts from six of the animals were negative after treatment, the other results were erratic.

Conclusions

(1) It would appear from the results given in the above tables of egg-counts and from the improvement observed in the general condition of the animals treated that phenothiazine has distinct merits as an anthelmintic for strongyles in horses.

(2) The average weight of the horses treated in the above experiment was approximately 1,000 lbs., and the effective minimum dose was 30 grammes. This represents 1 gramme of phenothiazine per 33 lbs. of body weight.

(3) In view of the fact that phenothiazine may be given in the feed of the horse with little previous preparation of the animal, it has obvious advantages over drugs requiring long preliminary fasting and more elaborate methods of administration.

(4) No evidence was obtained of any untoward reactions, and although slight malaise was observed in two or three animals, this may have been due to individual idiosyncrasy.

(5) The drug has the additional value that it does not interfere with the normal working of the horse.

(6) The foregoing conclusions suggest that regular periodic dosing with phenothiazine might provide a safe and easy method for the control, if not the complete eradication, of strongyles in horses.

Acknowledgments.—We desire to express our thanks to Lieut.-Col. C. G. Darley, D.S.O., Commanding Officer, 3rd Horse Cavalry Training Regiment, and to Major D. A. Gillmor, R.A.V.C., for the facilities to carry out this investigation.

* * * * *

Treatment of Equine Strongylosis by Phenothiazine

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At the suggestion of E. L. Taylor, D.V.Sc., D.V.H., M.R.C.V.S., Senior Research Officer of the Laboratory of the Ministry of Agriculture and Fisheries, Weybridge, it was decided to carry out trials at the Royal Army Veterinary Corps Laboratory to test the efficacy of the anthelmintic drug thiodiphenylamine, also known as phenothiazine, for the treatment of strongylosis in horses.

This drug has proved very effective against stomach worms in sheep and would appear to exert more effect than any preparation previously tried for the removal of worms from the large intestine of sheep. It was thought, therefore, that phenothiazine might prove an efficient expellant of strongyles from the horse.

Three horses were selected for these observations:

(1) No. 110. Bay Mare, 7 years old. Rider. Condition moderate.

(2) No. 47. Bay Mare, 7 years old. Rider. Condition moderate.

(3) No. 94313. Black Mare, aged. Rider. Condition poor.

For the purpose of this trial egg counts of the faeces were made by Stoll's method before and after the treatment, and were continued for 21 days after administration of the drug. The results of these counts are shown in table overleaf.

From the result of the egg counts as shown in the above table it will be noted that before treatment none of the horses gave very high counts and these animals were not regarded as acute cases of strongylosis. They were selected as the most suitable cases at our limited disposal for this observation.

The phenothiazine was supplied by Dr. Taylor in tablet and in powder form. In two instances the drug was administered by stomach tube and in the third by mixing with the food. When the tablets were used these were finely ground before administration.

RECORD OF TREATMENT AND EGG COUNTS

Subject.	Date.	Strongyle Eggs per Gramme.	Treatment and Remarks.
Horse No. 110	26.10.39	600	
	27.10.39	600	
	30.10.39	300	60 grammes phenothiazine in 1 gallon warm water per stomach tube.
	31.10.39	200	No parasites in faeces.
	1.11.39	0	*Strongylus edentatus* and *Strongylus vulgaris* present in faeces.
	2.11.39	100	" " "
	3.11.39	0	" " "
	4.11.39	0	" " "
	5.11.39 to 20.11.39	0	No parasites in faeces.
Horse No. 47	26.10.39	600	
	27.10.39	600	
	1.11.39	300	100 grammes phenothiazine in 1 gallon warm water per stomach tube.
	2.11.39	900	No parasites in faeces.
	3.11.39	100	" "
	4.11.39	200	*S. edentatus* and *S. vulgaris* in faeces.
	5.11.39	0	No parasites in faeces.
	6.11.39	0	*S. endentatus* and *S. vulgaris* in faeces.
	7.11.39 to 22.11.39	0	No parasites in faeces.
Horse No. 94313	14.11.39	100	
	15.11.39	100	
	16.11.39	200	60 grammes phenothiazine in food.
	17.11.39	100	No parasites in faeces.
	18.11.39	0	" "
	19.11.39	0	*S. edentatus, S. vulgaris* and *Trichonema* in faeces.
	20.11.39	0	" " "
	21.11.39	0	" " "
	22.11.39 to 7.12.39	0	No parasites in faeces.

On mixing with water phenothiazine tends to sediment rather rapidly, but we found that by keeping the suspension constantly stirred during administration no sediment remained when given by the stomach tube. The drug was given in one gallon of warm water.

The other method of administration consisted of mixing the drug with food. For this purpose a quarter bucket of warm bran mash was prepared and the powder well mixed with it.

Although the mare selected for this trial had been fasted for 24 hours previously she did not regard the feed favourably, ate about a third of the mash and refused to take more. When, however, a double handful of oats was added to the remainder of the mash she rather reluctantly finished it.

It has been suggested that horses may be induced to take the drug more readily by giving them small amounts of treacle, bran and oats for a few days previously and then mixing the powdered drug with this food when it is readily taken. In further trials it is proposed to employ this method.

As far as dosage is concerned, two horses received 60 grammes and one 100 grammes of phenothiazine. The smaller doses, judging from the egg counts, appeared to be just as effective as the larger ones, but as we were only dealing with comparatively light infestations the same rule may not apply to heavy invasions.

No ill effects were noticed after administration; there was no softening of the faeces, no rise in temperature and the appetite was unaffected.

In each case three worm egg counts were carried out on separate days before administration.

Red-tinged urine was observed in each horse on the day after the administration of the drug. This pigmentation disappeared in about 48 hours. The red coloration is due, not to the presence of blood, but to a colour reaction derived from the drug.

The horses were prepared by fasting for 24 hours before administration, after which they received only warm bran mashes for a further 24 hours, and then reverted to ordinary diet.

A naked-eye search for parasites was carried out on all dung passed after the drug was given. No special apparatus was employed for this purpose, the pellets merely being broken down and carefully examined. A few parasites were observed in all three cases, these appearing upon the second or third day after administration and persisting until the fifth day.

Specimens were despatched for classification to Dr. Taylor, who identified them as *Strongylus edentatus, Strongylus vulgaris* and *Trichonema.* In two of the horses two species of Strongyles were observed only, in the third horse all three species were present.

Egg counts were taken and observations were recorded for a period of 21 days after administration.

It will be seen from the tabulated record that in addition to the expulsion of adult worms the drug was completely effective in removing ova of Strongylidae from the faeces, as in the counts taken prior to administration eggs were present in, at any rate, appreciable numbers. It must be noted that in our previous experiences with the use of anthelmintic drugs for the treatment of strongylosis of horses, although a reduction in the number of ova in the faeces was brought about, after a time the number again increased. It will, therefore, be necessary to make observations over a longer period than has been done in these experiments and to consider the advisability of giving a second or even a third dose of the drug.

As an anthelmintic for strongylidae in horses the results appear to be very encouraging and would justify the carrying out of trials upon a more extensive scale. In comparison with other anthelmintics used for the treatment of strongylosis in horses phenothiazine appears up to the present to have a decided advantage in being harmless to the patient.

The question as to whether or not a purgative could be usefully employed in combination with this drug is a matter for further consideration.

Trial of Phenothiazine in Ascarid Infestation in Dogs

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Subject.—Six terrier puppies, all of one litter, and all reared together; and a second group of four puppies also of one litter.

Treatment.—After overnight starvation, phenothiazine was administered in tablet form to each puppy with the exception of two out of the first six which were kept as controls.

Egg Counts.—Daily examinations for ascaris eggs were made for a period prior to and after treatment and the number of eggs per gramme of faeces estimated.

Worm Counts.—All faeces passed during three days after treatment were examined for worms and on *post-mortem* examination the whole of the intestinal tract was searched.

Results

The data which were collected are set out in the accompanying table and show little or no effect on ascarid infestation in puppies as a result of treatment with doses of phenothiazine varying from 6 to 12 grammes.

This result was unexpected as many hundreds of ascarids were passed by a horse which was treated with phenothiazine at about the same time.

All of the puppies tolerated the drug well and in no instance were there any symptoms of intoxication. The urine was highly coloured, however, and in at least one instance the faeces showed traces of the drug.

WHY DO CELLS DIVIDE?

"So much is known about how a cell divides that our ignorance of why it divides is apt to be overlooked. There is probably no single answer that applies to every type of cell. Even if it is agreed that when it has attained a certain size a cell divides and multiplies, one must inquire whether external or internal causes make it swell to this size, and whether the causes act by stimulation or by removal of some restraint. In approaching this question from a theoretical standpoint most minds unconsciously assume that, whether delivered from within or without, the cell requires a prod. Nevertheless, in their attitude towards the cause of multiplication of tumour cells a great many authorities imply, if they do not actually state, that all cells would continually go on dividing if they were not subject to some restraint. Either attitude is reasonable but it is as well to be clear about one's assumptions. Explants of tumour tissue begin to grow *in vitro* after a very short or even no latent period, and Doljanski and Hoffmann regard this as evidence of the unique position of tumour tissue with regard to the growth-inhibiting mechanism of the organism. No better evidence of the failure of the body to inhibit growth can possibly be obtained than that afforded by the behaviour of the tumour and its metastases in their natural abode. This failure, however, tells one nothing of the cause of the perpetual division of the tumour cell. The fact that growth starts without delay in tissue culture makes the untutored suspect that these cells carry a ready-made stimulus within them, whereas normal and embryonic cells must wait for one to be engendered, and that this positive stimulus is as little restrained by the culture medium as it is by the body."—*The Lancet* (June 29th, 1940).

Table of Data on the Effect of Phenothiazine in Puppies Infected with Ascarids

Pup No.	Weight in lb.	Dose in Grammes.	Before Dosage. No. of Days on which Egg Counts were made.	Before Dosage. Average.	Before Dosage. Fluctuation.	After Dosage. No. of Days on which Egg Counts were made.	After Dosage. Average.	After Dosage. Fluctuation.	Worms Passed.	Worms Found *Post-mortem.*
A1	10½	6	46	5,300	24,000– 2,400	9	2,700	3,600– 900	2 immature	4 (1 immature)
A2	10¾	7	14	6,100	13,200– 1,500	5	6,600	19,000–3,600	None	19 (8 immature)
A3	12½	12	20	8,150	47,000– 3,100	13	4,700	7,100–1,000	3 immature	6 (3 immature)
A4	9	12	46	6,300	17,000– 1,600	9	4,500	9,800–2,100	None	5 (3 immature)
A5	10	Not dosed	33	6,300	20,100– 2,500	—	—	—	—	18
A6	12	Not dosed	16	7,300	22,000– 2,700	—	—	—	—	5
B1	9¼	6	14	5,200	1,400–12,000	7	1,400	800–2,100	None	2 (1 immature)
B2	13	12	14	3,280	500–10,100	7	980	400–1,900	None	4 (2 immature)
B3	12	12	14	3,400	1,100–10,000	7	1,600	700–3,300	None	9 (6 immature)
B4	11	6	14	1,900	200– 9,100	7	450	100–900	1	3 (immature)

B1 passed 6 worms during the 14 days' observation before dosing, and B2 passed 1 worm during the same period.

ECONOMY IN THE USE OF DRUGS

The *British Medical Journal* of June 14th, 1940, draws attention to irregularities in importation and great increase in price of ergot preparations. This is another example reminding us that war-time conditions call for the strictest economy in the use of drugs. Our patients must have the maximum benefits from drug therapy but without wastage. Saving of drugs can be made by careful selection and more particularly by limiting prescriptions so that little or no unused medicine is left over at the termination of cases.

H.M. STATIONERY OFFICE PUBLICATION

The undermentioned has been published recently.

	Price net s. d.	*Post free* s. d.
Statutory Rules and Orders, 1940: Imported Cattle (Marking) Order, 1940, Amendment Order, August 17th, 1940	0 1	0 2

THE VETERINARY RECORD
September 7th, 1940.

ANTHELMINTICS

DURING the past few months trials have been made with phenothiazine in the control of parasitic infestation in the domestic animals. An account of the trials carried out by various workers is published in this issue of the *Veterinary Record*. The drug is not new for it was first prepared in 1885, though its parasiticidal properties were not recognised till 1934. Experiments were carried out with the drug in this and other countries following an observation by Knipling in 1938 that phenothiazine given in small doses prevented the development of hornfly larvae in the faeces of cattle.

The results of these trials are of such importance that the use of phenothiazine in the control of parasitic infestation with certain helminths is likely to represent a great advance. We are as yet ignorant as to how the drug acts. It is important to note that it has a pronounced effect on strongyloid worms in the large intestine of the horse and also on trichostrongyloid worms in the fourth stomach of the sheep. Further, with the worm *Trichostrongylus axei*, complete removal is effected from the fourth stomach of the sheep while it appears to have no action on the same species in the stomach of the horse. All worms, however, are not equally affected by the drug. It seems to be particularly successful in removing "red worms" in the horse and trichostrongyloid worms in the fourth stomach of the sheep. In addition, it is decidedly effective against *Ostertagia, Haemonchus* and *Cooperia*, though with *Nematodirus* the results have been less promising. Again, with *Ascaris*, the results in the horse are markedly good, but are somewhat less so in the pig, while in the dog it would appear that the drug is almost completely ineffective. These results provide evidence of the need for further investigation into the action of the drug.

Phenothiazine has several marked advantages over many of the other drugs in common use in the control of parasitic infestations. Its very high efficiency in removing from the alimentary tract many of the species of parasites known to cause extensive damage, is outstanding. It is true that large doses appear to be necessary, but the drug is comparatively cheap. Experiments indicate that there is a wide margin between the therapeutic and and toxic doses for most species. There is evidence that the drug may produce toxic symptoms, especially in horses, pigs and goats, but for all practical purposes, if the prescribed doses are used and the administration is carried out as recommended, the chances of harmful results are negligible. With many other drugs used in the control of internal parasites, preparation and after-treatment of the subject are often essential and cause much inconvenience; these measures appear to be unnecessary with phenothiazine, which, in itself, is a great advantage in favour of its use.

While more experimental and field work is desirable, there is no doubt that in phenothiazine we have a most valuable product, the use of which should do much to control many of the parasitic infestations from which our domestic animals, especially sheep and horses, suffer. It is also noteworthy that, in addition to the immediate effects of the drug on the worms in the alimentary canal and the consequent immediate benefit to the host following their removal, the use of phenothiazine, even in slight infestations, appears to be beneficial, as is shown by the increase in weight following its administration.

It is important for our readers to note that phenothiazine is a relatively simple organic chemical compound, that is, its composition is universally known and it is not in any sense a proprietary remedy, but is one that can be prepared by any firm of manufacturing chemists. Its application in field practice, in the light of what has been stated above in regard to its specific effects on particular parasites in certain hosts, must needs be restricted, however —at this stage, at all events—to skilled veterinary workers.

ABSTRACTS

[PHENOTHIAZINE AS AN ANTHELMINTIC FOR THE REMOVAL OF INTESTINAL WORMS FROM SWINE. Swanson, L. E., Harwood, P. D., and Connelly, J. W. (1940.) *J. Amer. vet. med. Ass.* **96**. 333-338.]

Swanson, Harwood and Connelly publish some preliminary data obtained from a number of experiments performed to determine the anthelmintic efficacy of phenothiazine for the removal of gastro-intestinal parasites from swine. Following a brief review of the literature dealing with the chemical, the authors discuss the materials and methods used in their experiments. The data presented indicate that phenothiazine, in doses far below those which proved even slightly toxic, removed approximately 60 per cent. of the mature ascarids present in pigs at the time of treatment, but that the drug was much less effective against larval and well-grown but sexually immature ascarids. The drug appears to be as effective as oil of chenopodium, except in cases where only a few worms are present, and it possesses several practical advantages over other anthelmintics in that it has a low toxicity, a greater efficacy in heavily infested than in lightly infested animals, is easy to administer and is active against more than one species of worm parasite as it is the only known medicament which is effective for the removal of nodular worms from swine. Its low efficacy in removing ascarids when only few worms are present is a decided disadvantage.

The authors also found that recrystallised phenothiazine was more effective as an anthelmintic than conditioned phenothiazine, which has been proposed for use as an insecticide. They do not consider it advisable to recommend the drug unconditionally at the present time until further tests have been carried out although they propose a schedule of doses which are intended only for experimental use. J. N. O.

[THE EFFECT OF COPPER SULPHATE AND FERRIC SULPHATE ON COCCIDIAL OÖCYST OUTPUT IN FEEDER LAMBS. Christensen, J. F. (1940.) *J. Amer. vet. med. Ass.* **96.** 478-480. (1 fig., 2 refs.).]

During a study of " feedlot " coccidiosis in lambs in central Nebraska, an opportunity was afforded to test the effect of ingestion by the host animals, of small amounts of a solution of copper sulphate and ferric sulphate on the level of a natural coccidial infection.

This test was suggested by the observation of Spindler that daily administrations of small quantities of a dilute aqueous solution of these chemicals to three spring lambs in Maryland produced a significantly lower average level of oöcyst discharge during the early natural infection than was noted in three control lambs. In the present test it was desired to determine whether this reduction in oöcyst discharge might be similarly produced in lambs confined to feedlots for fattening, by having available small amounts of these chemicals for daily consumption during the first weeks of confinement, when coccidiosis is most likely to develop.

Twenty range lambs from a single shipment from New Mexico were separated into two groups of ten on the day following their arrival at the Nebraska feedlots. These groups were placed in adjacent pens but their feed and water containers were well separated. The two groups came from the same flock and were assumed to have equal susceptibility to coccidiosis. They received identical rations contaminated with infected faecal material. It was assumed that the two groups picked up potentially equal infection and that any differences observed in the average oöcyst discharge were produced by the administration of the chemicals.

The test solution was prepared by dissolving 2·3 ounces each of powdered copper sulphate and powdered ferric sulphate in 3·15 quarts of tap water. A cloudy, brownish precipitate formed and settled, and only the clear supernatant fluid was used. From the first day of confinement throughout the duration of the test, 2 ounces of this solution was added daily to the drinking water of the lambs in one pen, each lamb thus receiving theoretically an average of 1·5 drachms of the solution daily, while the control lambs received none.

Oöcyst counts to measure the coccidial infections in the two groups were made every three days for a period of five weeks, which was considered sufficient to cover the period of maximum oöcyst discharge. The manner of preparing the faecal samples for examination and count is described. A figure is given indicating the comparative records of the oöcyst counts in the two groups. The levels of infection in the two groups were similar for the first 16 days showing " the low-grade oöcyst discharges characteristic of chronic coccidial infections in healthy lambs." Thereafter, however, during the remaining period of the test, the level of the oöcyst discharge of the treated lambs was significantly lower than for the lambs receiving no chemical. The untreated lambs, however, despite the higher average count, remained normal in health except for one lamb which suffering from diarrhoea, passed faeces showing 78,000 oöcysts per c.c. of faeces. The average for the entire group including this specimen was 18,000 per c.c. of the special suspension.

It is admitted that the numbers involved in the present experiment are too few to justify any final conclusion but it is suggested that it is possible that the use of a copper sulphate - ferric sulphate mixture, preferably mixed as a powder with feed, might prove to be a valuable supplement to proper nutrition and management in eliminating the ever-present danger of outbreaks of clinical coccidiosis in certain parts of America.

L. E. W. B.

Reference—Spindler, L. A. : Effect of ferric sulphate and copper sulphate on coccidiosis in lambs. *N. Amer. Vet.* XX (1929) **5.** 33-38.

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[SPECULATIONS ON THE INCIDENCE OF ANTHRAX IN BOVINES. Clark, R. (1938.) *J. S. Afr. vet. med. Ass.* **9.** 5-12.]

Most outbreaks of anthrax in South Africa are sporadic in nature and few animals die in each outbreak. It is argued that most of the cases are due to massive infection caused by ingestion of contaminated bones or carcases owing to pica. If mass outbreaks do occur vaccination is valuable but many of the good results attributed to this may easily be due to the limitation of the infection to the animal or animals first affected, which appears to be a frequent result in unvaccinated herds.

P. S. W.

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[THE IMMUNISATION OF BOVINES AGAINST LAMSIEKTE. Mason, J. H., Steyn, H. P., and Bisschop, J. H. R. (1938.) *J. Amer. vet. med. Ass.* **9.** 65-70.]

A series of five injections of 10 c.c. at three weekly intervals of formol toxoid of *Cl. botulinum* types C and D (D for the first three injections and C for the last two) produced a demonstrable immunity against lamsiekte. Half-yearly injections of 5 c.c. of each toxoid maintained this immunity. During 1937-1938, 201 cattle were immunised and none died of lamsiekte. Of 14 control cattle four died.

P. S. W.

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[THE EFFECT OF INTERMITTENT STARVATION ON CALCIFICATION, FOOD UTILISATION AND TISSUE COMPOSITION. Kellermann, J. H. (1939.) *Onderstepoort J.* **12.** 321.]

Experiments were conducted on rats in an investigation of the effect of short intermittent fasts (two days in seven) on bone calcification, food utilisation and tissues. The results, analysed statistically, showed there were no significant differences between the percentage ash of the femurs of males compared with females or of controls compared with fasted animals. Further, there were no significant differences found between controls and fasted animals in respect of food utilisation, but males made uniformly better use of their food than females. Intermittent periods of fasting had no effect on the composition of liver and muscle tissues.

A. E.

NOTES AND NEWS

The Editor will be glad to receive items of professional interest for inclusion in these columns.

Diary of Events

Sept. 16th.—Meeting of the Editorial Committee, N.V.M.A., at 36, Gordon Square, W.C.1, 4 p.m.
Sept. 18th.—Meeting of the Western Counties Division, N.V.M.A., at Exeter, 2 p.m.
Sept. 20th.—Last day for Entries for Miss Aleen Cust Scholarship.
Oct. 10th.—R.C.V.S. Committee and Council Meetings.
Oct. 11th.—R.C.V.S. Committee and Council Meetings.

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PERSONAL

D.S.O. for Lt.-Colonel A. A. Comerford, M.R.C.V.S.

His colleagues in the profession will be proud and gratified to learn of the award of the Distinguished Service Order to Lieutenant-Colonel Augustine Ambrose Comerford, Royal Artillery, Territorial Army, for " gallant and distinguished services in action in connection with the recent operations "—to quote the announcement appearing in *The London Gazette* of August 23rd, 1940.

Lt.-Colonel Comerford, M.R.C.V.S., resides at Potton, Bedfordshire. He served throughout the last war in the Royal Army Veterinary Corps and in the R.A.V.C. (T.A.) for many years afterwards. He at one time held the appointment of D.A.D.V.S., East Anglian Division.

On the reduction of the establishment of Veterinary Officers caused by mechanisation he transferred voluntarily to the Royal Artillery and was subsequently gazetted Lieutenant-Colonel in that regiment on May 22nd, 1939.

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Forthcoming Marriage.—Balls—Rush.—The engagement is announced between Donald Vernon Balls, eldest son of Mr. and Mrs. V. S. Balls of Wimbledon Common, London, and Izabel Scott Rush, only daughter of Mr. E. Rush, Oporto, Portugal, and Madame M. Broadbent Mena, of Lisbon, Portugal.

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R.C.V.S. OBITUARY

Bradshaw, Capt. J. T. C., Winterbourne, St. Mathias', Babbacombe Road, Torquay. Graduated London, July 17th, 1909. Died August 27th, 1940.

Sullivan, Hugh Augustus, Lt.-Colonel A.V.C. (retd.). Graduated London, December 17th, 1891. Died August 24th, 1940.

Lieutenant-Colonel H. A. Sullivan, late A.V.C.

We regret to record the death at Worthing on August 24th of Lt.-Colonel Hugh Augustus Sullivan, late A.V.C.

The deceased officer was born at Ootacamund, India, on May 25th, 1868, and qualified M.R.C.V.S., at the Royal Veterinary College, London, on December 17th, 1891.

He was commissioned as Veterinary-Lieutenant on March 13th, 1892, and proceeded one year later to India, where he served until 1899. From November, 1899, until November, 1901, he was engaged in the war in South Africa and received the Queen's Medal with three clasps. From 1902 until 1907 he again served in India and he retired with the rank of Major on April 17th, 1912. In October, 1912, he assumed duty as Assistant Director of Veterinary Services to the Home Counties Division, an appointment which he held until he was invalided from the army in 1914.

Lt.-Colonel Sullivan married in 1899, and is survived by his widow, to whom we extend our sincere sympathy.

The Late Mr. R. L. Cornell, B.Sc., M.R.C.V.S.

(An Appreciation by one of his Former Teachers)

Cornell was the best student of his year, in a class some of whom have since succeeded in impressing themselves much more conspicuously on the notice of the profession. Retiring, gentle, modest, and friendly-disposed, his personal ambitions were restrained and his capacity for asserting himself was reduced to such point that his talents probably never found an environment congenial to their full development. Reflection at this moment upon the careers of men who showed his degree of early promise cannot but excite wonder whether those who had it in their power to guide the destinies of the profession at the stage when Cornell graduated strove as they ought to have done to nurture to self-confidence and fruitfulness such as had his ability and his temperament.

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Staff Captain E. A. W. Dixie

We deeply regret to learn of the death in action at Cassel, a few miles inland from Dunkirk, of Captain Edward A. W. Dixie, a student of the Royal Veterinary College, who passed his third examination in July, 1939.

In the course of a moving tribute published in the current issue of the *Veterinary Journal*, it is stated that Captain Dixie was a Territorial Officer and as such was mobilised at the outbreak of war. " Whatever the task in hand," says the writer (a professor at the College), " Dixie would bring all his energies to bear upon it and he entered the new field of endeavour with all the zest he had displayed in his academic career."

" Captain Dixie was Anti-Tanks Officer to the 145th Infantry Brigade (Oxford and Bucks). His regiment, which was holding a position in the village of Cassel, was attacked by a large force of enemy tanks on the morning and afternoon of May 27th. Captain Dixie was firing a gun himself and, in his Adjutant's words, 'He put up a truly magnificent show, his guns accounting for a large amount of enemy tanks.' This is exactly what I should have expected of him." Shortly after, when moving out for a rest, he was mortally wounded.

" Captain Dixie was 23 years old and his life was full of promise of great things," the tribute proceeds. " He will be deeply mourned by staff, students and lay personnel of the College, for he was kind and courteous to all. The country and the profession can ill afford to lose such men." All our own readers will desire to join in the expression of deepest sympathy then extended to the mother of this gallant veterinary student.

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LEGAL NOTES

Veterinary Surgeons Act: Successful Dublin Summonses by Veterinary Council

Manufacturers of Remedy for Contagious Abortion in Cows Fined £200

The *Irish Times* of August 29th reports that Certus Chemical Industries, Ltd., Pearse Street, Dublin, were fined £100 on each of two summonses charging them with practising or holding themselves out as practising or being prepared to practise veterinary surgery or veterinary medicine, contrary to Section 47 of the Veterinary Surgeons Act of 1931, at Saucerstown, Swords, Co. Dublin, on February 5th last, and at Kiloternan, Co. Waterford, on July 3rd.

Ten guineas costs and expenses were given against them.

Evidence was given by Messrs. Colm Lawless, Saucerstown, and Maurice Fitzgerald of representatives of the company having treated their cattle for contagious abortion by a remedy stated to have been manufactured by the company.

Mrs. Dore, director and secretary of the company, said that they had received testimonials from farmers and colleges all over the country. Their agents were instructed not to treat cattle, but only to sell the remedy.

In reply to Mr. C. Lavery, K.C., who, with Mr. Andreas O'Keefe (instructed by Messrs. Arthur Cox and Co.), appeared for the Veterinary Council, she said that it was not for her to say whether the douche, which was in powder form, contained 87 per cent. of ordinary salt. That was a matter for the chemist.

Captain P. Cowan, solicitor, for the company, said that the defendants never had held themselves out as practising, or being prepared to practise, veterinary medicine or surgery.

The Justice said that 87 per cent. of this "infallible" remedy for the terrible disease of abortion in cows was ordinary common salt. This was a farming community and one depending on veterinary science and the proper treatment of cattle.

Captain Cowan said that in fairness to his clients he must say that Mr. Lavery only had suggested to a witness that this remedy contained 87 per cent. of salt. They had not been given an opportunity to refute that.

He added that his instructions were to appeal against the decision.

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Control of Animals in Air Raids: New Defence Regulations

We reproduce below the text of three new Regulations (25A, 25B, and 79B) recently made under Order in Council and issued by the Ministry of Home Security as Statutory Rules and Orders, 1940, No. 1134—adding these Regulations to the Emergency Powers Defence (General) Regulations, 1939.

Power to Control Animals in the Event of Hostile Attack

25A.—(1) The Secretary of State may by order make such provision for the control of animals and vehicles drawn by animals as he considers expedient with a view to securing the public safety or maintaining public order in the event of hostile attack.

(2) Any such order may be made so as to apply either throughout Great Britain and Northern Ireland or to any areas therein.

(3) A constable in uniform may inspect any animal to which any such order applies and the harness or other equipment attached thereto for the purpose of ascertaining whether the order is being complied with, and, if the animal is in motion, any person driving, leading or otherwise in charge of the animal, shall stop the animal on being required so to do by the constable and render all reasonable assistance to the constable for the purpose of the exercise of his powers under this paragraph.

Stray Dogs

25B.—(1) A person taking possession of a stray dog may, instead of returning the dog to its owner or taking it to a police station in accordance with subsection (1) of section four of the Dogs Act, 1906, as amended by any subsequent enactment, take the dog to any animal post within three miles from the place where the dog was found and inform the person in charge of that post where the dog was found.

(2) Where a dog is taken to an animal post under the foregoing paragraph, the person in charge of the post shall:—

(*a*) forthwith take such steps as may be reasonably practicable to trace the owner of the dog and restore it to him;

(*b*) within three days next following the day on which it was taken to the post, take the dog to the nearest police station, unless it has been restored to its owner;

and where a dog is taken to a police station in pursuance of this paragraph, it shall be treated as if it had been seized by a police officer in pursuance of section three of the Dogs Act, 1906.

(3) The person in charge of an animal post shall enter in a register kept by him the following particulars as respects any dog taken to the post in pursuance of this Regulation, namely:—

(*a*) a brief description of the dog;

(*b*) the date on which it was received by him; and

(*c*) the manner in which it was disposed of;

and shall cause the said register to be open to inspection at all reasonable times by any member of the public.

(4) In this Regulation the expression 'animal post' means any post established, under arrangements approved by the Minister of Home Security, for dealing with animals in the event of hostile attack.

(5) This Regulation shall not extend to Northern Ireland.

Power to Slaughter Dangerous and Injured Animals in the Event of Hostile Attack

79B.—(1) In the event of the occurrence of hostile attack in the vicinity, any constable may—

(*a*) with a view to securing the public safety or maintaining public order, slaughter any animal which appears to him to be—

(i) at large or out of control; and

(ii) dangerous or seriously injured;

(*b*) with a view to preventing the wastage of food suitable for human consumption, slaughter any animal which appears to him to be seriously injured;

Provided that the power conferred by sub-paragraph (*b*) of this paragraph shall not be exercised, if the owner of the animal is present and objects.

(2) A chief officer of police, if he considers it necessary or expedient so to do for the purpose of—

(*a*) securing the public safety or maintaining public order; or

(*b*) preventing the wastage of food suitable for human consumption,

in the event of hostile attack, may authorise in writing any person being a duly registered veterinary surgeon or an officer of an approved organisation to exercise the powers conferred on a constable by the foregoing paragraph.

(3) The power to slaughter an animal conferred by or under this Regulation shall include power—

(*a*) to cause or procure the animal to be slaughtered by some other person;

(*b*) to enter, and to authorise any such other person to enter, upon any land for the purpose of the slaughter; and

(*c*) to remove and dispose of the carcase, or cause it to be removed and disposed of:

Provided that—

(i) except where an animal is slaughtered in a place to which the public have access, the power to remove the carcase shall not be exercised if the owner is present and objects; and

(ii) any person exercising the power to dispose of a carcase shall comply with such directions (if any) as may be given to him by the chief officer of police.

(4) In this Regulation the expression "approved organisation" means any organisation formed for the promotion of the welfare of animals and for the time being approved for the purpose of this Regulation by the Minister of Home Security.

(5) This Regulation shall, in its application to Northern Ireland, have effect as if for the reference to the Minister of Home Security there were substituted a reference to the Secretary of State.

. . . . .

In connection with Regulation 79B (*Power to slaughter dangerous and injured animals in the event of hostile attack*), the following comments are made in a communication addressed by the Home Office to chief officers

of police, for their assistance in the interpretation and enforcement of the Regulation:—

Paragraph (1) confers certain powers on a constable to slaughter animals (*a*) with a view to securing public safety or maintaining public order, or (*b*) to prevent wastage of food. (This latter provision is intended for cases where animals suitable for food have been injured in an air raid and would become useless for human consumption unless slaughtered immediately).

Paragraph (2) enables chief officers of police to confer similar powers on registered veterinary surgeons or officers of organisations approved by the Minister of Home Security. The purpose of this power is to enable full use to be made of the local units of the National A.R.P. Animals Committee, which the Minister of Home Security has approved for the purpose under paragraph (4) of the Regulation. This Committee, as explained in A.R.P. Department Circular 267/1939 of October 7th, 1939, is organised to relieve the police and local authorities of much of the responsibility for dealing with animals in air raid conditions. It will be noted that any authority given by the police under paragraph (2) of the Regulation must be given in writing and it is suggested that the following form should be used:—

"*Authority to act under Regulation* 79B *of the Defence (General) Regulations*, 1939

To A.B.

In pursuance of Regulation 79B of the Defence (General) Regulations, 1939, I hereby authorise you during, or within 12 hours after, the occurrence of hostile attack in the vicinity, to slaughter any animal which appears to you to be seriously injured and, if the animal is slaughtered in a place to which the public have access, to remove the carcase or cause it to be removed therefrom;

Provided that you are not authorised to slaughter any animal which appears to you to be neither at large nor out of control nor dangerous nor in such condition as to be likely, in the circumstances, to cause public disorder or disturbance, unless food suitable for human consumption would be likely to be wasted if the animals were not slaughtered, and the owner, if present, raises no objection.

C.D.,

Chief Constable of....."

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FOWL CHOLERA IN SCOTLAND

In a recent announcement the Ministry of Agriculture states that outbreaks of fowl cholera have recently been diagnosed in the counties of Dumbarton, Stirling and Clackmannan. This disease attacks all types of domestic poultry and some wild birds and is capable of causing severe losses. All poultry owners are advised to investigate immediately any unusual mortality by sending one or two specimen carcases to a poultry laboratory for examination.

To prevent the further spread of infection, the following precautions should be adopted by all owners of poultry in or near the above-mentioned counties.

When possible purchase live birds only from sources which are known to be free from disease.

With every newly purchased lot of birds mix one or two low value birds of the home flock and keep them together in isolation for 14 days. Any illness or death among them should be investigated without delay.

Make sure that all crates and other receptacles used for birds are at once thoroughly disinfected, in compliance with the Poultry Markets and Receptacles (Disinfection) Order of 1936.

Fowl cholera is not an egg-borne disease. An advisory leaflet (No. 19) on fowl cholera is obtainable post free on application to the Ministry of Agriculture, Lindum Hotel, Lytham St. Annes, Lancs.

MINISTRY OF AGRICULTURE NEWS SERVICE

Sugar Beet Growers Beat Records.—An encouraging picture of the home sugar industry was given by Sir Francis Humphrys, Chairman of the British Sugar Corporation, at the Annual Meeting. Farmers last season produced the record average yield of 10·14 tons of beet per acre, compared with the average of 8¾ tons for the past ten years. In spite of exceptional frost, that often made lifting difficult, and in spite of transport difficulties, 99·5 per cent. of the crop was delivered and gave more sugar at a time when the need for home supplies was greatest. The 1939 crop gave us not only 500,000 tons of sugar but 300,000 tons of dried and molassed sugar beet pulp, equivalent in feeding value to oats, and 3,000,000 tons of crowns and leaves, that ton for ton are of higher feeding value than turnips, swedes and mangolds. This saved the country additional shipping space and foreign exchange as well as saving us the high cost of insurance and convoying.

Sir Francis Humphrys paid a tribute to farmers and seedsmen for their enterprise in growing at home the seed we had to import until a few years ago. Arrangements have been made to produce at home all our seed requirements for a normal season. As a measure of prudence a reserve of seed has been created in America.

Sugar Beet Tops.—The feeding value of sugar beet tops is often under-estimated. When clean and fresh, this value is equal to the same weight of swedes and a 10-ton crop of washed beet gives 8 to 9 tons of tops. They may be reckoned as equivalent to three-fifths of an acre of turnips. Sugar beet tops come at a time when natural decay is slow and, therefore, retain their freshness up to the new year.

Use.—They can be used in four ways: (1) feeding to sheep and sows on the field; (2) carting off to stock a pasture; (3) for silage; (4) for ploughing-in. Folding with sheep is the most convenient and economical method disposal. One acre of tops, supplemented with a grass run will keep 90 to 100 ewes for a week. Folding entails less waste than free range and a change to grass also makes for greater cleanliness. One cart-load daily is usually fed to 20 to 30 cows when the tops are carted and spread on pasture. The clamp is the cheapest and most convenient form of silo for beet tops, but good silage can also be made in pits where drainage is satisfactory. A clamp usually about 14 feet wide, is made on the surface of the ground and carried up to 7 to 8 feet, the empty carts going over the heap lengthwise. After rounding off, a cover of straw is laid on and immediately earthed over to the depth of 1 foot. The heap will settle to 3 to 4 feet, and if cracks appear in the soil covering they should be filled up. As a rule, 3 to 4 feet of length is allowed for each acre of crop.

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AGRICULTURAL RESEARCH COUNCIL

The Committee of Privy Council for the Organisation and Development of Agricultural Research has appointed to fill vacancies on the Agricultural Research Council, caused by normal retirement, Sir Robert Blyth Greig, LL.D., D.Sc., and, after consultation with the President of the Royal Society, Professor W. W. C. Topley, M.D., F.R.C.P., F.R.S., Professor E. J. Salisbury, D.Sc., F.R.S., and Professor T. J. Mackie, M.D., D.P.H., M.R.C.P.E., F.R.S.E. The committee has also reappointed Sir William Cecil Dampier, Sc.D., F.R.S., and Mr. John Smith, M.R.C.V.S., D.V.H., for a further term.

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A BACTERICIDAL BACTERIAL EXTRACT

Commenting that when so many workers are preoccupied with the study of chemotherapy by means of sulphonamide compounds it is interesting to find that substances which will kill bacteria are also being looked for in quite another direction, the *British Medical Journal*, in an annotation appearing in December, 1939,

continues: "An effort demanding exceptional patience and optimism which has nevertheless had astonishing success is described in a series of papers by R. J. Dubos.* He started with the assumption that bacteria may exist which are capable of attacking Gram-positive cocci or some of their constituents, and employed in searching for them a method which has in fact already yielded micro-organisms capable of breaking down pneumococcal polysaccharide. A mixed sample of soil with certain mineral additions was maintained under suitable conditions of humidity and temperature until its decomposition was considered almost complete, and then fed for two years with suspensions of staphylococci, streptococci, and pneumococci. Since these bacteria furnished the only pabulum, only those soil organisms which could attack them would continue to proliferate, and presumably their capacity for doing so would be accentuated by adaptation during so long a period. At the end of it a sporing aerobic Gram-positive bacillus was isolated in culture from the soil which formed a substance capable of lysing staphylococci. This substance was liberated by the disintegration of the bacilli in ageing cultures, and could be obtained in a comparatively pure state by acidification, which precipitated it, and re-solution in a neutral medium. Although earlier preparations so obtained contained a protein, further purification yielded a highly active extract which was protein-free. The properties of this substance are quite unexampled. It attacks not only staphylococci but all Gram-positive cocci which have so far been tested; on the other hand, it is entirely without action on Gram-negative bacteria. Pneumococci, which are most susceptible to its action, are killed in a short period by a concentration of 0·002 mg. per c.cm., and their growth is inhibited by the presence of less than one-hundredth of this amount. The lysis which results from its action is regarded as secondary, death having been caused by an action the nature of which is uncertain, although there is evidence of interference with the dehydrogenase system of the bacterial cell. Not only is this bactericidal action exerted *in vitro*, but the substance protects mice against large multiples of a minimum lethal dose of pneumococcus culture, even when its administration is postponed for several hours after infection. This is, of course, a much more remarkable property than any *in vitro* action, and at once stultifies any comparison with the action of violet dyes, to which there is some resemblance in the fact that only Gram-positive bacteria are attacked. It is not too much to say that these observations open a new field in the study of bacterial metabolism. It has long been known that some bacteria form substances more or less antagonistic to the growth of others—pyocyanin is the most familiar and best authenticated example—but the vigour, scope, and specificity of the effect demonstrated by Dubos are something entirely new. It may well be that susceptibility to the products of other bacteria is confined to a few pathogenic species, fastidious in their growth requirements; on the other hand, who knows what further strange phenomena may be brought to light by patience and a few pots of soil?"

*J. exp. Med. (1939.) 70. 1, 11, 249.

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PATHOLOGICAL EFFECTS OF VASOPRESSIN

"Our knowledge of the functions of the posterior pituitary is still incomplete," stated the *Lancet* recently. "While recent work has plainly implicated the antidiuretic fraction in the physiological control of water metabolism, the pressor activity remains of uncertain importance; yet the two activities have never been obtained in separate fractions. The classic proofs for the endocrine function of a gland are also difficult to apply to the posterior pituitary owing to its dependence on nerve control, though the effects of overdosage of vasopressin may give some indication of the results of a pathological hyperfunction of the gland itself.

"Dodds and his colleagues[1] demonstrated the production of gastric ulcers in rabbits and other animals following the injection of large quantities of vasopressin. They were able to demonstrate[2] that the action is due to the pressor effect of the extract which diminishes the visceral blood-flow and leads to the inhibition of gastric and pancreatic secretion. The ulcers are caused by the action of the acid stomach contents on the ischaemic mucosa, thus explaining the fact that they are most easily produced in the rabbit whose stomach is normally never empty. They also demonstrated[3] the production of a macrocytic anaemia in rabbits by the same means, though the cause of this is still doubtful. These findings did not at first seem of great practical importance owing to the very large doses of vasopressin required, but Idris Jones[4] has since described a case with hypochromic anaemia, hypertension, decreased glucose tolerance and achlorhydria which he suggests was an instance of posterior pituitary hyperfunction. Noble, Rinderknecht, and Williams[5] were able to demonstrate large amounts of pressor and antidiuretic activity in this patient's urine, the excretion of which ceased at the same time as the symptoms. Another important effect of vasopressin overdosage is the kidney lesions, described by Byrom[6] and Liu and Noble.[7] These are of more immediate clinical interest since they are suggestive of those found in toxaemias of pregnancy. The large quantities again necessary to produce the lesions experimentally do not rule out the connection since Byrom[8] found that oestrone or chorionic gonadotrophin will sensitise the rat to the toxic effects of vasopressin. These facts offer some explanation of the onset of the disease during pregnancy. The water-retention and hypertension found in toxaemia of pregnancy had in any case suggested to earlier authors that the disorder was caused by posterior pituitary hyperfunction and there have been claims that pressor and antidiuretic activity has been found in the blood of such patients. These claims have, however, not been supported. The latest is that of Teel and Reid[9] who find antidiuretic activity in the urine of pregnant women suffering from toxaemia. The quantitative basis of these experiments is open to objection owing to the recent demonstration[10] that blood and urine extracts are capable of augmenting the antidiuretic action of vasopressin by diminishing its rate of absorption. These facts, which have been ably summarised by Liu,[11] all point to the conclusion that the experimental effects produced by vasopressin overdosage do simulate clinical conditions."

1. Dodds, E. C., Noble, R. L., and Smith, E. R., *Lancet*, 1934. 2. 918.
2. Cutting, W. C., Dodds, E. C., Noble, R. L., and Williams, P. C., *Proc. R. Soc.* B., 1937. 123. 27.
3. Dodds, E. C., and Noble, R. L., *Nature*, 1935. 135. 788.
4. Jones, E. I., *Lancet*, 1938. 1. 11.
5. Noble, R. L., Rinderknecht, H., and Williams, P. C., *Ibid.*, p. 13.
6. Byrom, F. B., *J. Path. Bact.*, 1937. 45. 1.
7. Liu, S. H., and Noble, R. L., *J. Physiol.*, 1938. 93. 13P.
8. Byrom, F. B., *Lancet*, 1938. 1. 129.
9. Teel, H. M., and Reid, D. E., *Endocrinology*, 1939. 44. 297.
10. Noble, R. L., Rinderknecht, H., and Williams, P. C., *J. Physiol.*, 1939. 96. 293.
11. Liu, S. H., *Chin. Med. J.*, 1939. 55. 448.

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Swine fever has at last been got under control in Aberdeenshire, and the Orders forbidding sales in the city and county, after being in operation for several months, were revoked recently.

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By an amendment of the Poisons Rules made under the Pharmacy and Poisons Act the ban on the use of strychnine as a vermicide is removed. Under the new regulation a quantity, not exceeding 4 oz. of strychnine, may be supplied to a person producing a written authority issued by a county war agricultural executive committee.

CORRESPONDENCE

Letters to the Editor should reach the Office not later than by the first post on Tuesday morning for insertion in following Saturday's issue.

The views expressed in letters addressed to the Editor represent the personal view of the writer only and must not be taken as expressing the opinion or having received the approval of the N.V.M.A.

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RED CROSS AND VETERINARY CHARITIES FUND

To the Editor of the Veterinary Record

Sir,—Just over a month ago the writer started a fund to help primarily the Red Cross. At the suggestion of several friends contributions were also invited for veterinary charities. Veterinarians who possess gold or silver medals or other gold or silver articles were asked to contribute them to the fund or to make a cash contribution instead. In the *Veterinary Record* of August 10th the fund was referred to in "Notes and News."

The total amount received to date is approximately £17, of which £13 is for the Red Cross and £4 for the Victoria Veterinary Benevolent Fund; this distribution between the two charities is that suggested by the individual donors. Ten veterinarians have contributed, the amounts received from individuals varying from 5s. to rather more than £3.

The response can only be described as disappointing. If every veterinary surgeon and veterinary student in possession of medals were to surrender them we should raise several hundred pounds. It was hoped that an appeal which invites the sacrifice of medals by those who during their student days or later were fortunate enough to be awarded them would meet with a widespread response. Those who qualified at the London College alone during the past 25 years could themselves contribute £100 with ease. And what of those who graduated at the other veterinary colleges of Great Britain? Are there no medallists from this source or is it that they hide their medals under a bushel? If so, now is the time to bring them to light. If modesty prevents any medallist from sending in his or her medals, anonymous contributions would be gratefully received.

Every gold medal will realise approximately 23s. and every silver medal just over 3s. The need is great. I await with confidence the hundreds of medals which will arrive following the publication of this letter; I hope the charities will not be disappointed and that the profession will make a response worthy of its best traditions.

A list of contributors will be published as soon as the exact amounts obtained from the sale of medals are received from the refiners.

Yours faithfully,
E. G. White.

Research Institute in Animal Pathology,
Royal Veterinary College,
"The Beeches,"
Streatley, Berks.
August 29th, 1940.

* * * * *

ANTI-BLAST EAR PROTECTORS

To the Editor of the Veterinary Record

Sir,—Would you please grant space so that the attention of members of the N.V.M.A. may be drawn to a highly approved form of ear pad protecting the tympanum against blast?

A very efficient protection against blast as it affects the tympanum of the ear has been devised and placed before the public.

Made from latex, multicelled, moulded to form a hollow hemisphere which encloses the whole ear, the "pads" are reinforced and held together as a pair by an elastic band which is adjustable to persons of all ages. The combined weight is about 2 oz. Though these form an efficient protection as aforesaid, normal conversation can be carried on by the wearer.

My principal object in introducing this is indicated by the following: according to information received from refugee friends from Poland and the Low Countries, the damage done to the tympanum of the ear by blast was probably one of the most common injuries sustained by the civilian population of these countries.

The cost of the appliance is very moderate.

Yours faithfully,
George Dykes.

Small Animal Clinic,
6, Douglas Street,
Glasgow, C.2.

DISEASES OF ANIMALS ACTS, 1894 to 1937, and AGRICULTURE ACT of 1937 (PART IV)

Summary of Returns of Confirmed Outbreaks of Scheduled (Notifiable) Diseases

Period.	Anthrax.		Foot-and-Mouth Disease.		Parasitic§ Mange.		Sheep Scab.	Swine Fever.	
	Outbreaks confirmed.	Animals attacked.	Outbreaks confirmed.	Animals slaughtered as diseased or exposed to infection.	Outbreaks confirmed.	Animals attacked.	Outbreaks confirmed.	Outbreaks confirmed.	Swine slaughtered.
	No.	No.	No.	No.	No.	No.	No.	No.	No.
Period 16th to 31st July, 1940	26	31	—	—	—	—	1	205	153
Corresponding period in ...									
1939	29	34	—	—	—	—	1	138	146
1938	24	26	2	321	—	—	1	41	19
1937	26	42	6	400	1	1	1	26	16
Total 1st January to 31st July 1940	322	365	19	2,850	15	30	118	2,538	1,584
Corresponding period in									
1939	510	555	44	5,652	31	70	157	1,338	978
1938	535	592	157	20,261	42	70	105	377	267
1937	457	556	15	3,646	87	124	131	688	427

Note.—The figures for the current year are approximate only. § Excluding outbreaks in Army Horses.

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[No. 37]

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